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13. ABSTRACT (Maximum 200 Words)
The objectives of this study, "Development of a computer Decision Support System for Women with BRCA1 or BRCA2 Mutations" was to create a decision support system that provided individualized information about the expected benefits of alternative cancer risk reduction strategies for women with either a BRCA1 or BRCA2 mutation. The project was comprised of three phases: 1) development of the education booklet, 2) development of the Decision Support System (DSS), and 3) randomized controlled trial of the DSS. The primary outcome of the trial was decision satisfaction. Secondary outcomes included knowledge of the effects of alternative management options on cancer risk, anxiety and depression, and behavior and behavioral intentions. Women who were in the Decision Support System arm reported higher satisfaction with their decisions than did women in the control arm (mean Decision Satisfaction Score 31.2 vs. 26.2, p=0.04). In addition, higher decision satisfaction at follow up was associated with cancer anxiety at baseline and having had breast cancer or a prophylactic mastectomy prior to enrollment. The results of this trial are currently being submitted for publication. In addition, we are currently developing a methodological review highlighting the questions raised by this trial and similar trials.

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Introduction

The goal of "Development of a Computer Decision Support System for Women with BRCA1 or BRCA2 Mutations" was to develop a decision support system to provide individualized information about the expected benefits of alternative cancer risk reduction strategies for women with either a BRCA1 or BRCA2 mutation. For decision-making about cancer risk reduction by women with BRCA1 or BRCA2 mutations to be truly informed, decisions must be consistent with a woman's personal preferences and values. Such decisions ultimately can only be made by the woman involved - she is the only one able to adequately value the trade-offs among the benefits, risks, and costs of the alternative management strategies. The objective of this project was to develop and evaluate a Decision Support System (DSS) that will improve informed decision making by providing women with tailored, simplified information about the expected health outcomes of alternative decisions. The DSS was based on a Markov model so that it could easily be updated with new epidemiological evidence to provide women with the most accurate and up-to-date information about their risk and expected outcomes. Print outs of the information simulations from the DSS were individualized to each woman for review and guidance with health care treatment decision making processes.

Body

Phase One: Development of Educational Booklet

To identify cancer risk information desired by woman with a BRCA 1/2 mutation, we conducted five focus groups from the fall of 1998 to the spring of 1999. The focus groups were composed of women who had come from the Cancer Risk Evaluation Program (CREP). CREP is a multidisciplinary clinical program that provides breast cancer risk assessment, genetic counseling, and BRCA1 and BRCA2 testing. Initially we had planned to include only women with a mutation in the focus groups. Because, there were a limited number of mutation positive women, we also included women seeking counseling about BRCA1 and BRCA2 testing, regardless of their mutation status.

In each of the focus groups, participants discussed the information they would want to help their decisions about cancer risk reduction and other concerns about BRCA1 and BRCA2 mutations relevant to their needs. There was striking consistency across focus groups in the information desired by women considering or undergoing BRCA testing. Several women came to the CREP because of a strong family history of breast and/or ovarian cancer, which they feared might be due to a genetic mutation. Most women had several female family members who died of breast cancer, and many were close to the age/stage of their lives that their relative(s) were when they became ill. Some women wished to know their BRCA status so that they could take every potentially effective preventative measure possible (e.g., prophylactic mastectomy, prophylactic oophorectomy, chemoprevention therapy). Other participants' motivation was to obtain the knowledge of their BRCA status so that their children would be informed of their own cancer risk.

The focus groups identified the efficacy, side-effects, and cost of cancer surveillance and prevention options as important informational needs. In addition, insurance discrimination, cost, their futures, and the presentation of the information that was shown to the participants were important issues. Privacy and the protection of BRCA test results were paramount concerns for this population. Cost was also an issue derived in part from the high cost of testing and in part because of their uncertainly of whether insurance companies will

cover testing, surveillance or preventive surgery. Insurance coverage was concerning because of perceived lack of legislation protecting a woman from losing her insurance coverage if she is found to carry a mutation.

Many of the women were certain that they will develop breast and/or ovarian cancer, the only uncertainty being when this will happen to them. They were interested in understanding more about their risk over time- particularly, in relation to their ability to care for their children. Finally, the women offered advice on the method of presenting the information conveying their risk information. It was widely felt that statistics were little more than numbers to them; they uniformly desired more visual representations of risk and benefit information, such as survival curves, pie charts, or other representation.

The information gathered from the focus groups was incorporated into the educational booklet used in Phase Three, the randomized controlled trial of the DSS. Entitled "Health Care Options for Women at Risk for Breast and Ovarian Cancer," (Appendix A) the booklet covers topics suggested by women who have either been counseled about being tested or have been tested for a BRCA1 or BRCA2 mutation. The illustrations completed by a medical illustrator at the University of Pennsylvania complement the text and aide in the understanding of the results of prophylactic surgeries. Drafts of the booklet were critically reviewed several times by an expert panel at the University of Pennsylvania, including Barbara Weber, MD, Andrea Eisen, MD, Jill Stopfer, MS and Kathleen Calzone, MSN. Importantly, these reviews led to the addition of several sections including breast and ovarian cancer screening, hysterectomy, and implications for family members.

The book was then sent to 12 Cancer Risk Evaluation Program (CREP) patients to review for any content or organizational suggestions. Reaction from these women was overwhelmingly positive, and there were very few changes suggested. Minor grammatical and structural changes were made to clarify some content, but the booklet was otherwise unchanged. In August 2000, the text and illustrations were published in a spiral bound book by the University of Pennsylvania Department of Marketing and Strategic Support and used during the randomized control trial (RCT) that began in November 2000 and ended June 2003.

Since the publication of the booklet, we have added supplemental information. This supplement includes updated information about BRCA1 and BRCA2, and incorporates comments from women in the RCT. Since the

booklet was originally created for women who tested positive for the gene mutation but did not have breast cancer, many of the comments came from mutation positive women who have also been diagnosed with breast cancer. The supplement clarifies which information is specific to BRCA positive women, and which information also relates to BRCA positive women with breast cancer (Appendix A) using recently published data in this field. [1-5]

Phase Two: Development of the Decision Support System

Part A: Development of Decision Analytic Model

Throughout the duration of this study, the decision analytic model has been extensively revised, refined and expanded. These improvements included:

1. Inclusion of tamoxifen as an alternative breast cancer prevention therapy. This expansion required incorporating additional health states for other outcomes affected by tamoxifen, including venous thromboembolism and endometrial cancer.[6-8]
2. Because the majority of women who are found to carry a mutation in BRCA1 or BRCA2 have been previously diagnosed with breast cancer and these women still face many of the same decisions about cancer risk reduction as women without a cancer diagnosis (e.g. prophylactic surgery), the investigator team felt it was important to include women with a prior diagnosis of breast cancer in the trial. Thus, we substantially revised the model to allow tailoring to the presence or absence of a previous diagnosis of breast cancer. Because survival following a diagnosis of breast cancer depends upon the characteristics of the cancer (in particular, stage and node status), we developed individual survival functions for Stage 1 and Stage 2 node positive and node negative breast cancer, further tailoring the model simulations for women with a prior diagnosis to the characteristics of their individual tumors. Initial feedback from our expert panel suggested the survival curves for node positive women might create sufficient distress that would interfere with informed decision making. Thus, we excluded node positive breast cancer patients from the trial.
3. Development of statistical functions for breast cancer, ovarian cancer and hip fracture incidence.

4. Development of appropriate coronary risk prediction models from Framingham data. These logistic regression models were derived from primary data with the assistance of Henry Glick, PhD.[9, 10]
5. We have validated the model by comparing the estimated life expectancy from the simulation model using population based incidence rates for breast and ovarian cancer with data from the National Center for Health Statistics. The life expectancy of a 50 year old woman at average cardiac risk who selects no therapy from the simulation is 31.68 years compared to 31.70 years estimated by the National Center for Health Statistics.
6. Identification of probability density functions for: effect of prophylactic mastectomy on breast cancer risk; effect of prophylactic oophorectomy on breast cancer risk; effects of HRT on risks of breast cancer, CHD, osteoporosis; effects of tamoxifen on risks of breast cancer, endometrial cancer and venous thromboembolism. [6, 11-15]
7. Insertion of an age function that will allow the model to run age specific simulations for each age between 20 and 70.
8. Incorporation of data from relevant epidemiological studies including the effect of prophylactic mastectomy on breast cancer risk in high risk women, effect of prophylactic oophorectomy on breast cancer risk in BRCA 1/2 mutation carriers, the risk of a second breast cancer in BRCA 1/2 mutation carriers, the effects of tamoxifen on risks of breast cancer, endometrial cancer and venous thromboembolism, the effect of HRT on risk of CHD and breast cancer from the Women's Health Initiative. [6-17]

As a result of the focus groups of women from CREP, the investigator team and expert panel all felt that showing the effect of alternative management strategies on breast cancer incidence was necessary to help women make decisions about cancer risk reduction strategies. Thus, we revised the model to allow accurate calculation of cumulative incidence curves for breast cancer among women without a prior diagnosis of breast cancer. To minimize information overload, we initially show women only the curves for overall mortality and breast cancer incidence, the ovarian cancer curves are shown if a woman has indicated interest.

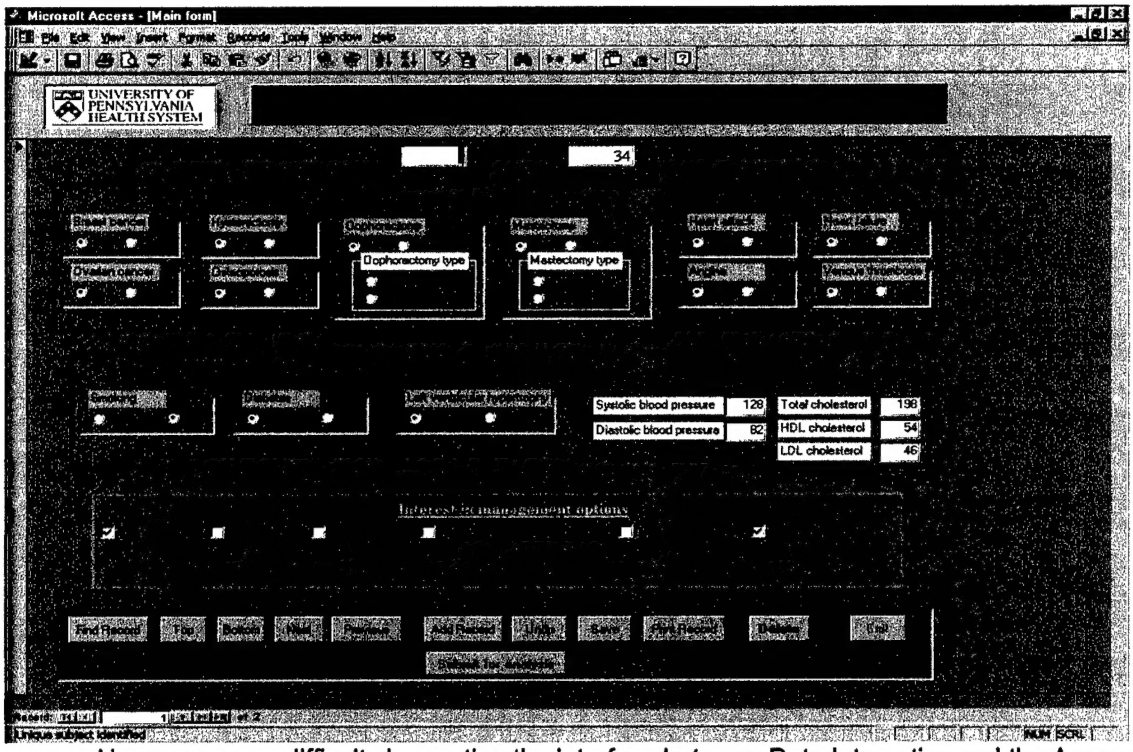
Part B: Assessment of Format Effects

Using the data from the surveys conducted in past years, as reported in the 1999 annual report, the survival curve materials have been adapted to the specific context relevant to women with BRCA mutations. This involved developing text that explains the concept of survival curves and how they should be interpreted (Appendix D). In order for the curves to be clear and organized, we developed a method of presenting the curves that allows each woman to see her options individually as well as together.

Each decision aid includes treatment option information as well as breast cancer incidence information. A baseline (no intervention) survival curve is fixed to a divider while the treatment options, each printed on transparencies, can be superimposed over the baseline curve. This layering effect allows the women to see the difference in survival between having no treatment (baseline) and the various treatment options, which can also be compared to each other. This method enables women to clearly distinguish which option gives her the best survival rate over time.

Part C: Development and completion of the Computer Interface

Between 1999 and 2000, the design and function of the computer interface for the decision support system was refined. This process required numerous meetings with project staff and with a focus group of nurses who have an interest in breast cancer research. After numerous iterations, a final design was implemented in Microsoft Access (shown below in the figure). Access supports ActiveX objects through its extensive data model, and interfaces with the Data Interactive product from TreeAge Software. The interface for this system is shown below:



However, some difficulty in creating the interface between Data Interactive and the Access application forced us to develop another system in parallel, so as not to delay the project. This second system provides an interface to the Markov model in DATA, using the interface builder in DATA software. Early in 2000, there were some technical problems with the system, which resulted in a temporary halt in recruitment. Fortunately these problems have been fixed, and we were able to carry on with recruitment.

Phase Three: Randomized Controlled Trial of Patient Decision Support System

The Randomized Control Trial (RCT) began with the enrollment of the first subject in November 2000. All questionnaires, booklet, decision aid, and model materials were developed, produced, and implemented successfully in the RCT. Eligible subjects are contacted through CREP once their results are disclosed. Eligibility criteria include women who are: between the ages 20-65, BRCA 1 or BRCA 2 mutation positive, have breasts and/or ovaries, and reside within a reasonable travel distance, by car, from the University of Pennsylvania.

The genetic counselors at the CREP inform the potential subjects about our study by offering them an introduction to the study letter (Appendix B). Individuals interested in the study are then told that the research coordinator will contact them with more information. Once the research coordinator is informed that there is an

eligible subject, she contacts the potential subject by phone. Once the subject agrees to enroll in the study another staff member opens a randomization envelope to determine whether the subject will be in the control arm (booklet only) or the intervention arm (booklet and decision aid). The booklet is sent to all subjects along with the questionnaire "Assessment of Risk Factors & Interest in Risk Reduction Options" (Appendix C), which the subject is asked to complete and mail back. Upon receiving the completed questionnaire the research coordinator contacts the subject to schedule a visit.

When the subject comes in for her visit she completes the "Baseline Questionnaire" (Appendix C). The research coordinator clearly stresses that while the information being presented is useful and represents a theoretical outcome of a woman like herself, it is not a certainty. The limitations of the research coordinator are also explained, noting that any specific health care questions or concerns be directed to a personal physician. The research coordinator asks the subject if there are any questions about the content of the booklet, and whether she found it to be useful. Any comments are recorded and incorporated in future booklet or decision aid updates. If the subject has been randomized to the control arm, her visit is complete. She is advised that she will be called in a month to complete a follow up questionnaire (Appendix C) with another staff member.

If the subject is in the intervention arm then the decision aid is reviewed next. To introduce the content of the decision aid the woman is asked to complete a practice exercise to ensure that she understands the concept of survival and incidence curves. Once the subject understands what she will be shown the research coordinator presents the individualized survival and incidence curves. The baseline survival curve, representing the subject's outcome if she took no action to change her cancer risk, is shown first. Next, she is shown a sample of the management curves. If the subject does not currently have breast cancer, she is next shown incidence curves in the same manner that she viewed the survival curves. Throughout the process, the subject is asked questions to ensure that she understands the curves as well as providing an opportunity for her to ask questions. The research coordinator answers questions covered in the pre-specified script, but addition questions are referred to counselors at CREP. After the decision aid has been reviewed the subject is told that another staff member will call her in a month to complete a follow up questionnaire.

To date, there have been 32 subjects enrolled in the study, 32 have completed and returned the "Assessment of Risk Factors & Interest in Risk Reduction Options" questionnaire, 30 have completed the interview session, and 27 have completed the follow-up telephone questionnaire. This results in a response rate of 84%.

Although, the recruitment rate is lower than we had envisioned, we have seen a major increase in subjects enrolled in the past year. As of January 2002 there were still only two completed interviews. This low recruitment rate is due to several factors. Low numbers include a slower than anticipated uptake of testing for the BRCA1 and BRCA2 mutations in general, and specifically among cancer free men and women. The majority of women who are testing positive for the presence of a BRCA1 or BRCA2 mutation have already been diagnosed with advanced breast or ovarian cancer, and are undergoing treatment. Thus the number of healthy women who are being tested in order to understand their personal and familial risks is small. In addition, we encountered technical problems with the DSS at the beginning of 2002, and this resulted in a temporary halt in recruitment.

We explored many possibilities to increase enrollment. Patients who tested positive for a mutation through the CREP before this study began were contacted to see if they were interested in participating. However, many had taken some action to manage their risk since being tested, making them not eligible for the study. Recently, CREP offered a no cost test to men and women in families with known mutations; this provided us with a new group of healthy women who were likely to be BRCA1 or BRCA2 mutation carriers. Another option involved the possibility of expanding to other hospitals with genetic testing programs within the Philadelphia area. Collaboration with the University of Pennsylvania-owned Pennsylvania Hospital has lead to a successful enrollment of eligible subjects. Collaboration with the Cancer Network, specifically Administrative Director, Jeanne Rogers, R.N., M.Ed. and coordinator Mary Sharon Rumsey, R.N., M.SN, which is part of the University of Pennsylvania Cancer Center, was also investigated as a possible means of recruitment, as was the possibility of expanding to other sites outside of Philadelphia. However, expansion to new sites would have had significant statistical and financial implications and was felt not to be feasible by the study investigators. Based on time constraints we choose to concentrate on sites located in the Philadelphia area.

Recruitment was enhanced by direct outreach to Ashkenazi Jewish communities, since BRCA1 and BRCA2 mutations are more frequent in this population.[16] Advertisements were placed in four local Jewish newspapers: Jewish Exponent, Main Line Times, Jewish Community Voice, and Jewish Voice. We also placed the ad in 15 local Jewish temple and synagogue newsletters. The advertisements ran for one to two months, and most of the temples and synagogues allowed us to run our ad for free in their newsletter.

In addition, outreach to other organizations was conducted over 2002 in attempts to further increase enrollment. In April of 2002 we posted an announcement about the study on Facing Our Risk of Cancer Empowered website's message board (www.facingourrisk.org). This site provides information and support for women who have or are at high-risk for the BRCA 1 or 2 mutations. At a past conference for young breast cancer survivors, sponsored by the organization Living Beyond Breast Cancer, we distributed flyers to members. Through these recruiting techniques we received a number of calls from women interested and willing to participate in the study. Unfortunately, a majority of interested women were ineligible because they either were not tested for the mutation or they lived too far to travel to our site.

Recently, we have been improving our response rate by following up with subjects who enrolled in the study but were unable to travel to our site for the initial meeting. The research coordinator has been traveling, by car, to subjects' homes to complete the meeting. This process has run smoothly and has been a positive experience. Subjects, especially those subjects receiving the intervention, seemed to be more relaxed and receptive of the information. This process could be considered for future similar studies.

Results of Randomized Controlled Trial:

Thirty-two women were enrolled in the trial, and 27 women completed follow-up. Three subjects dropped out because they were either unable to travel to the site or commit to a time for the research coordinator to travel to them, one subject was no longer eligible for the study, and one subject was not able to be reached to complete the follow-up questionnaire. Subject characteristics are reported in Table 1. None of the women reported having diabetes or high blood pressure. Four women reported having high cholesterol and six were unsure if they had high cholesterol- none were on cholesterol medication. No women had a prior myocardial infarction, had previously been diagnosed with angina, or took a medication for heart disease.

Table 1. Subject Characteristics

	Overall (n=32)	Intervention (n=16)	Control (n=16)	P-value
Mean age, yrs. (range)	43 (26-59)	45 (30-59)	42 (26-54)	
Caucasian (%)	100	100	100	-
Breast cancer (%)	48	46	50	0.84
College educated (%)	80	83	92	0.63
Cancer anxiety*	11.8 (6-23)	11.3 (6-19)	12.4 (6-23)	0.55
Information seeking preference#	13.2 (10-26)	12.4 (10-16)	14 (10-26)	0.22
Decision making preference #	39.4 (28-53)	40.2 (29-53)	38.6 (28-52)	0.57

* Revised Impact of Event Scale, higher score indicates higher cancer anxiety
# Autonomy Preference Index, higher score indicates greater desire for information or autonomy.

Baseline Attitudes and Knowledge:

Knowledge about risks of breast cancer, ovarian cancer and CHD, as well as the impact of intervention on those risks are reported in Table 2.

In general, women appeared to have relatively accurate

	Overall (n=27)	Control (n=14)	Intervention (n=13)	P-value
Chance of breast cancer by age 70 with mammograms only	67.5 (20-95)	69.3 (40-90)	65.9 (20-95)	0.69
With prophylactic mastectomy	9.5 (0-40)	6.7 (0-40)	13.5 (5-25)	0.09
With prophylactic oophorectomy	24.7 (0-80)	20.6 (0-50)	31.1 (5-80)	0.28
With tamoxifen	32.7 (0-60)	29.5 (0-60)	38.1 (20-50)	0.30
With HRT after menopause	43.7(5-95)	40.9 (5-80)	46.9 (20-95)	0.63
With raloxifene after menopause	35.2 (0-80)	32.4 (0-80)	39.3 (20-50)	0.53
Chance of ovarian cancer by age 70 with no surgery	50.3 (20-100)	37.3 (20-70)	65.8 (30-100)	0.005
With prophylactic oophorectomy	5.4 (0-20)	3.9 (0-20)	7.8 (0-20)	0.16

Table 2. Patient estimates of personal risk of cancer at baseline

perceptions of the risk of breast cancer and the effects of prophylactic surgery, tamoxifen or raloxifene on that risk. Perceptions of the risk of ovarian cancer were higher than those found in most studies of BRCA1/2 mutation carriers (and provided in the clinical counseling session). Women were asked to estimate their risk of heart disease with and without HRT or raloxifene but less than half of participants completed those items.

Intentions about future cancer risk related health care decisions were assessed by asking whether participants had previously used the intervention in question, were planning to use it in the next 6 months, or were planning to use it sometime after 6 months from now (Table 3). Prophylactic surgery prior to enrollment was relatively common with approximately 10% of women having undergone prophylactic mastectomy and 40% having undergone prophylactic oophorectomy. In addition, approximately 15% of women had taken tamoxifen prior to enrollment.

Table 3. Behavioral Intentions at Baseline

		Overall (n=32)	Intervention (n=16)	Control (n=16)	P-value
PM	Prior to enrollment	11.1	23.1	0	
	in next 6 months	14.8	0	28.6	
	in future	11.1	7.8	14.3	
PO	Prior to enrollment	40.7	46.2	35.7	
	in next 6 months	29.6	30.8	28.6	0.41
	in future	14.8	7.7	21.4	
Tamoxifen	Prior to enrollment	14.8	15.3	14.3	
	in next 6 months	7.4	7.7	7.1	
	in future	7.4	0	14.3	
HRT	Prior to enrollment	14.8	15.4	14.3	
	in next 6 months	11.1	15.4	7.1	
	in future	11.1	0	21.4	
Raloxifene	Prior to enrollment	11.1	23.1	0	
	in next 6 months	7.4	7.7	7.1	
	in future	11.1	0	21.4	

Effects of the Intervention:

The primary outcome of the trial was decision satisfaction. Secondary outcomes included knowledge of the effects of alternative management options on cancer risk, anxiety and depression, and behavior and behavioral intentions. Decision satisfaction was measured with a twelve item scale that included all items from two previously published scales: the Satisfaction with Decision Scale and the Decisional Conflict Scale, located in the follow-up questionnaire (Appendix C). All items were coded so that higher scores indicated great decision satisfaction. This 12 item scale had high internal consistency (Cronbach's alpha 0.86). Knowledge was measured by asking participants to estimate their lifetime risk of breast and ovarian cancer with and without alternative management options. Anxiety and depression were measured with two instruments: the Intrusion Subscale of the Revised Impact of Event Scale which measures cancer related anxiety and the Hopkins Symptom Checklist 25 which contains subscales measuring general anxiety and depression. Behavior and behavioral intentions about alternative management options were measured by asking participants to select the decision that best matched their current situation. Response options included: did not consider, decided against, still considering, planning to have in the future, have had or am scheduled to have in the next 6 months.

Decision Satisfaction

Women who were in the Decision Support System arm reported higher satisfaction with their decisions than did women in the control arm. This association was present in univariate analysis (mean Decision Satisfaction Score 31.2 vs. 26.2, p=0.04) and increased in magnitude after adjusting for baseline differences in demographic characteristics and prior cancer and prophylactic surgery decisions (Table 4). Adjustment for baseline levels of cancer anxiety (as measured by

Table 4. Effect of Decision Support System on Decision Satisfaction#

	Coefficient	SE	P-value
Decision Support Intervention	9.67	2.14	<0.0005
Baseline Cancer Anxiety*	0.68	0.22	0.007
Breast history			
No cancer, no prior PM	-	-	-
Prior cancer, no prior PM	9.38	4.55	0.06
Prior cancer and prior PM	12.46	2.78	0.001
Ovarian history			
Prior PO	-9.79	2.56	0.002

Adjusted for age, education, and marital status.
* Change in decision satisfaction for each one point increase in anxiety

the Revised Impact of Event Scale) did not affect the strength of the association between the Decision Support System and decision satisfaction. However, baseline cancer anxiety level modified the effect of the Decision Support System on decision satisfaction with significantly greater benefits seen among women who had lower levels of anxiety than among women who had higher levels of anxiety (Table 5). This interaction between baseline anxiety and treatment group on decision satisfaction was statistically significant whether anxiety was analyzed as a continuous variable (p-value =0.03), in quartiles (p-value =0.04), or as a dichotomous variable (e.g. above median vs. equal to and below median, p=0.01). The effect of the Decision Support System was not modified by age, education, marital status, prior cancer or prophylactic surgery history, or preferences for information or autonomy in medical decision making.

Table 5. Effect of Decision Support System on Decision Satisfaction according to Baseline Level of Cancer Anxiety#

	Mean Difference in Decision Satisfaction Scores between Intervention and Control Arm
Baseline Cancer Anxiety*	
Lowest quartile	14.2
Second quartile	13.7
Third quartile	6.78
Highest quartile	2.7

Adjusted for age, education, marital status, prior cancer and prophylactic surgery history.

In addition to the Decision Support System, higher decision satisfaction at follow up was associated with cancer anxiety at baseline and having had breast cancer or a prophylactic mastectomy prior to enrollment. Having had a prophylactic oophorectomy prior to enrollment was inversely associated with decision satisfaction at follow-up. Age, education, marital status, and preferences for information or autonomy in medical decision making were not associated with decision satisfaction.

We then explored the association between the Decision Support System and different domains of decision satisfaction. First, we reconstructed the two published scales related to decision satisfaction – the Satisfaction with Decision Scale (items f,i,j,k,and l) and the Decisional Conflict Scale (items a,b,c,d,e,g,h). These scales had reasonable internal consistency with a Cronbach's alpha of 0.76 for the Satisfaction with Decision Scale and 0.79 for the Decisional Conflict Scale. Interestingly, the Decision Support System was more strongly associated with

reductions in scores on the Decisional Conflict Scale (adjusted mean difference - 7.86, p=0.001) than scores on the Satisfaction with Decision Scale. (adjusted mean difference 1.98, p=0.08). In addition, we used principal components analysis to assess the presence of multiple domains within the overall 12 item scale. Three separate components were identified, with Eigen values of 5.38, 1.92 and 1.70 respectively. Table 6 reports the rotated loadings of the different items on the three components. Based upon these loadings we constructed three subscales, A (items g,h,j,k,and l), B (items a,b,c,) and C (items d,e,f,i). Subscale B corresponded to the decision uncertainty subscale of the Decisional Conflict Scale (items a, b, c) so we refer to it as the Decision Certainty Subscale. It had high internal consistency (Cronbach's alpha 0.86). Subscale A also had a high internal consistency (Cronbach's alpha 0.88) and we called this the Decision Resolution Subscale. Subscale C had somewhat lower internal consistency (Cronbach's alpha 0.74) and we called this the Informed Decisions Subscale.

Table 6. Principal Components Analysis of Decision Satisfaction Scale

	1	2	3
Eigen value	5.38	1.92	1.70
a. Decision hard to make	0.39	0.70	0.30
b. Unsure what to do	-0.03	0.95	0.03
c. Clear which choices are best	0.40	0.78	-0.06
d. Aware of management options	0.13	0.07	0.85
e. Know benefits of management options	0.41	0.42	0.56
f. Satisfied that adequately informed	0.10	-0.04	0.85
g. Know risks of management options	0.64	-0.08	0.30
h. Making an informed choice	0.93	-0.05	0.06
i. Satisfied these are my decisions to make	0.01	0.46	0.54
j. Expect to carry out my decisions	0.82	0.24	0.20
k. Decisions consistent with personal values	0.93	0.15	0.15
l. Decisions best possible for me personally	0.87	0.36	-0.01

Women in the Decision Support System arm had significantly high decision certainty (adjusted mean difference 4.27 p-

Table 7. Impact of Decision Support System on Decision Resolution

	Coefficient	SE	P-value
Decision Support Intervention	4.28	1.15	0.002
Baseline Cancer Anxiety*	0.27	0.12	0.03
Breast history			
No cancer, no prior PM	-	-	-
Prior cancer, no prior PM	4.16	2.44	0.11
Prior cancer and prior PM	6.97	1.50	0.001
Ovarian history			
Prior PO	-5.67	1.38	0.01
Marital status (Married vs. unmarried)	3.32	1.75	0.08
Education			
Less than college	-	-	-
College	-4.05	1.75	0.04
Graduate school	-2.91	1.85	0.14

Adjusted for age

* Change in decision resolution for each one point increase in anxiety

value =0.01) and decision resolution (adjusted mean difference 4.18 p-value =0.001) than women in the control arm. However, there was no difference in the Informed Decisions Subscale between the two groups (mean difference 0.80, p-value =0.50). In addition, several other factors were significantly associated with scores on the Decision Resolution Subscale, including baseline cancer anxiety, prior cancer and prophylactic surgery history, and education (Table 7). These factors were not significantly associated with scores on the Decision Certainty or Informed Decisions subscales.

Knowledge:

Women in the Decision Support System arm did not differ significantly from women in the control arm in their estimates of the effect of alternative management options on cancer risk, although there was a trend towards women in the Decision Support arm reporting higher estimates of the effect of interventions on cancer risk. (Table 8). Women in both the Decision Support and control arms continued to have difficulty completing the risk estimation items with approximately a third of women leaving each item blank. The level of missing data did not differ between study arms.

Table 8. Estimated effect of management options on cancer risk

	Intervention (n=13)	Control (n=14)	P-value
Change in breast cancer risk			
With PM	-50.3	-28.6	0.08
With PO	-38.5	-19.0	0.13
With tamoxifen	-30.0	-15.9	0.19
Change in ovarian cancer risk			
With PO	-45.7	-23.3	0.11

Anxiety and Depression:

Women in the Decision Support System arm did not differ significantly from women in the control arm in levels of anxiety or depression at follow-up. The adjusted mean difference in RIES score was 0.16 (p=0.89) between women in the intervention and control arms. Although women in the intervention arm did have lower scores on the HSCL (adjusted mean difference -2.89), this difference did not reach statistical significance (p=0.45).

Behavior and Behavioral Intentions:

Women in the Decision Support Arm did not differ from women in the control arm in their decisions about cancer risk management strategies. Among women who had not undergone prophylactic mastectomy prior to enrollment, 33% of women in the intervention arm and 53% of women in the control arm were considering undergoing mastectomy in the future. One woman in each arm had had or had scheduled a prophylactic mastectomy. Among women who had not undergone prophylactic oophorectomy prior to enrollment, 50% of women in the intervention arm and 38% of women in the control arm had undergone or had scheduled a prophylactic oophorectomy at the time of follow up. The remaining women in both arms were planning to undergo oophorectomy in the future. Among women who were not on Tamoxifen at the time of enrollment, 40% of women in the intervention arm and 54% of women in the control arm were considering taking tamoxifen in the future and 30% of women in the intervention arm and 9% of women in the control arm were planning to take tamoxifen in the future. None of these differences reached statistical significance (all p-values >0.20).

Conclusion

This project has demonstrated that the development of an individualized decision support system (DSS) that uses survival curves to provide information about expected outcomes of alternative management strategies is feasible and that the use of this DSS among women with BRCA1/2 mutations is associated with increased decision satisfaction without increased cancer anxiety. Furthermore, the effect of this DSS was largest for measures of decision resolution and decision certainty, rather than measures assessing knowledge or perceptions of being informed – suggesting that the mechanism by which the DSS affects decision satisfaction may be independent of its ability to improve accurate understanding of complex risk information. This finding is supported by the relative greater impact of the DSS among women with low levels of cancer anxiety at baseline, than among women with high levels of cancer anxiety at baseline. As suggested by trials of decision support in other settings, the use of the DSS was not associated with differences in the cancer risk management options that were chosen,

with the majority of women in both arms undergoing prophylactic oophorectomy and relatively few women in either arm undergoing prophylactic mastectomy.

The completion of this project has also highlighted several important methodological issues related to the development and implementation of decision support. In general, evidence changes rapidly in controversial, high stakes areas in medical care – the same areas which often appear appropriate for decision support. Thus, even when the ability to incorporate new evidence is planned into the decision support system, as was done in this trial, the perceived utility of decision support may change substantially over time as new evidence emerges that affects the level of uncertainty about the optimal decision. For instance, in the current trial, the publication of evidence demonstrating a greater than 95% reduction in ovarian cancer risk with prophylactic oophorectomy greatly reduced the sense of uncertainty about the use of prophylactic oophorectomy for women with BRCA1/2 mutations and affected the level of interest in decision support among women with BRCA1/2 mutations. This effect has been even more evident for the several trials of decision support for decisions about postmenopausal hormone replacement therapy. The publication of the Women's Health Initiative reduced the sense of uncertainty about these decisions and essentially ended trials of decision support (Nananda Col- personal communication). Importantly, this effect occurs even when the content in the decision support system can be updated to include the new information. Thus, randomized controlled trials of traditional, content based approaches to decision support are likely to be high risk as the need for decision support may no longer exist by the end of the trial. New decision support strategies are needed, potentially including the development of more generalizable methods to help patient's value trade-offs, understand risk or anticipate emotional reactions outside of any specific content area. Such strategies may be able to be moved quickly from one area of controversial, high-stakes decision making to another, as dictated by the available evidence. As demonstrated by this project, the use of survival curves to present risk information over time is a promising strategy that should be tested in this new model.

The results of this trial are currently being submitted for publication. In addition, we are currently developing a methodological review highlighting the questions raised by this trial and similar trials. Because this trial demonstrated that this DSS is beneficial for women who are found to carry BRCA1/2 mutations, we are

working with the clinical program at the University of Pennsylvania to devise methods to include and assess this intervention in clinical practice. This project has directly contributed to the successful application for Centers in Excellence in Cancer Communication at the University of Pennsylvania (K. Armstrong and J.S. Schwartz as co-investigators) and at the University of Michigan (P.A. Ubel, project leader). These P50 Centers logically extend the results of this project to improve cancer related decision making in several important areas, including the use of tamoxifen for breast cancer prevention and adherence to lifestyle modification for cancer risk reduction. Ultimately, this approach to individualized decision support has the potential to greatly improve decision satisfaction in many different high stakes decisions throughout the cancer continuum.

Key Research Accomplishments

Booklet Development

- Booklet completed and published August 2000.
- Booklet supplemental information created November 2002.

Computerized Decision Support System (CDSS) Development

- Linking of the model to the interface was completed in October 2000.
- The CDSS successfully implemented for use in the Randomized Control Trial November 2000.

Randomized Control Trial

- Decision Aid developed and published for use November 2000.
- Creation of advertisement strategies to target high-risk groups to increase enrollment October 2002.
- Expansion of recruitment to Pennsylvania Hospital September 2001.
- RCT completed June 2003.
    - 32 women enrolled in the study.
    - 32 women returned and completed assessment of risk questionnaires.
    - 30 women completed visits and baseline questionnaires.
    - 27 women completed follow-up telephone questionnaire.

Reportable Outcomes

Published Manuscripts (Appendix F)

- Armstrong K, Schwartz JS, Randall TC, Rubin SR, Weber BL. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA 1/2 mutations. Journal of Clinical Oncology, in press.

- Armstrong K, Schwartz JS, FitzGerald G, Ubel P. Effect of framing as gain vs. loss on hypothetical treatment choices: survival and mortality curves. Medical Decision Making, Jan-Feb 2002: 76-83.

- Armstrong K, Stopfer J, Calzone K, FitzGerland G, Coyne J, Weber B. What does my doctor think? Preferences for knowing the doctor's opinion among women considering clinical testing for BRCA 1/2 mutations. Genetic Testing. 2002; 34: 590-595.

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Appendix A

"Health Care Options for Women at Risk for Breast and Ovarian Cancer" Booklet

"Health Care Options for Women at Risk for Breast and Ovarian Cancer" Supplement

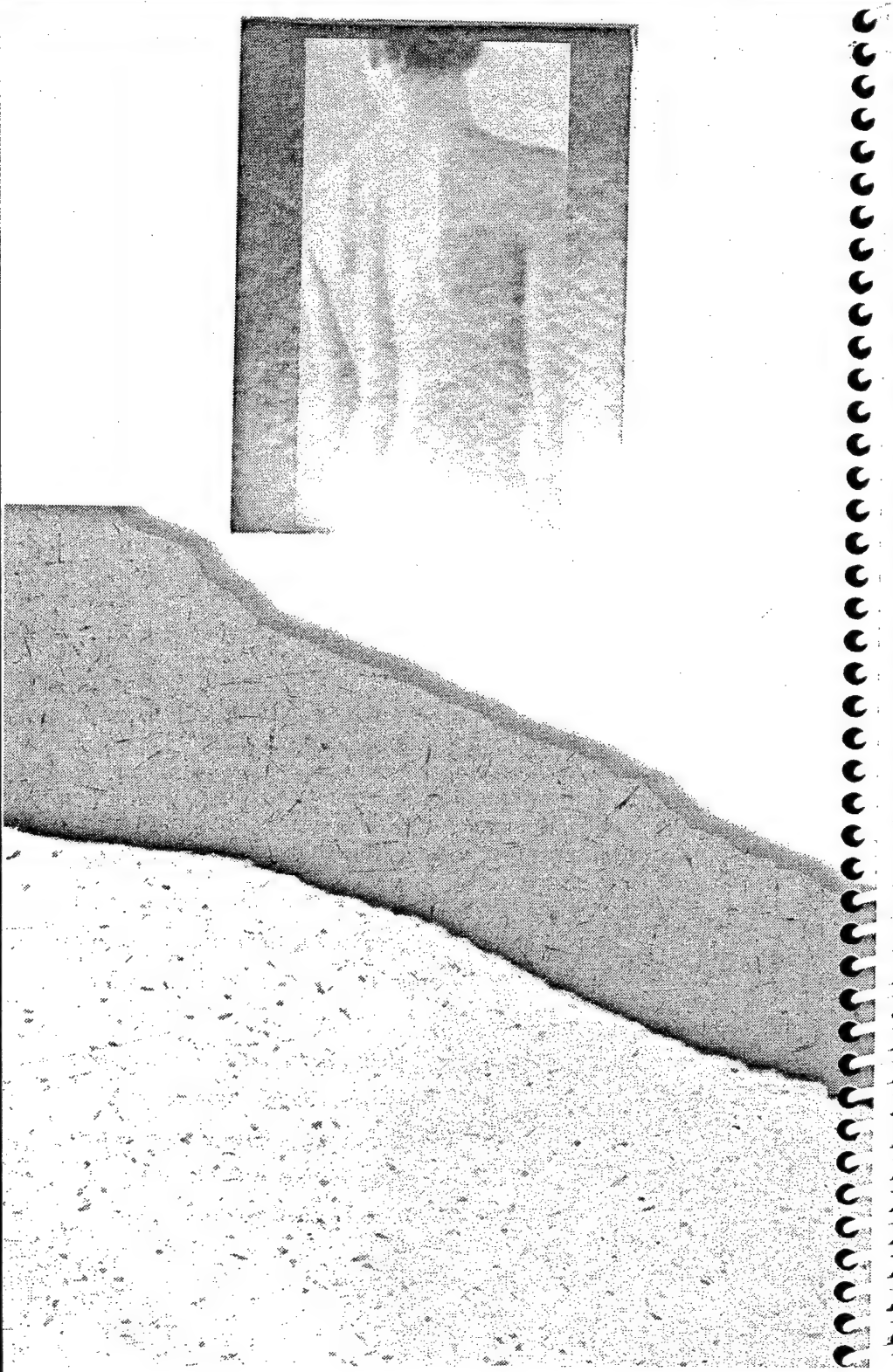
Health Care Options for Women at Risk for Breast and Ovarian Cancer

INTRODUCTION

This booklet was developed to help women with a BRCA1 or BRCA2 mutation make decisions about how to manage their risk of breast and ovarian cancer. The goal of the booklet is to provide information about all of the options available for managing breast and ovarian cancer risk as well as other issues related to carrying a mutation in BRCA1 or BRCA2. Because these decisions are complex and each woman's situation is different, each woman should discuss her personal situation with a physician, nurse, or genetic counselor who is knowledgeable about BRCA1 and BRCA2 as well as her regular health care provider. Above all, it is important that each woman makes an informed decision.

There are six sections in this booklet. Frequent breast and ovarian cancer screening is recommended for all women with a BRCA1 or BRCA2 mutation and is discussed in the first section of the booklet. The second section discusses prophylactic surgery – removal of the ovaries or the breasts prior to the development of cancer. Tamoxifen (Nolvadex), the only medication currently approved to reduce the risk of breast cancer, and oral contraceptives, which may reduce the risk of ovarian cancer, are discussed in the third section. The fourth section focuses on hormone replacement therapy and raloxifene (Evista), medications that are often considered at the time of menopause. The fifth section reviews the current knowledge about the effect of lifestyle, such as diet and exercise, on risk of breast and ovarian cancer. The last section discusses other implications of carrying a BRCA1 or BRCA2 mutation, including implications for family, insurance and confidentiality.

Because medical research moves quickly, new options for managing cancer risk may become available at any time. Regular contact with health care providers and specialized counseling programs, such as the Cancer Risk Evaluation Program, can help women with BRCA1 or BRCA2 mutations stay informed of the latest developments.



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I. FREQUENT CANCER SCREENING

The benefits of screening procedures for women with BRCA mutations have yet to be proven, and so far are based mostly on expert opinion. The types of studies needed to prove the benefits of these screening procedures may take years to become available, since researchers need to be able to follow women over time to see how these procedures affect long term outcomes. Since BRCA1 and BRCA2 were only discovered in 1994 and 1995, follow-up time for women with mutations has been limited. However, the screening recommendations are based on the known importance of early detection for cancer and what is known about individuals at average risk. Generally, cancer that is detected in earlier stages is more easily treated, and the likelihood of a cure is higher in these cases.

Breast Cancer Screening:

Breast Examination

- What is it?

Breast examination is a type of screening that involves either a woman checking her own breasts for lumps (self breast examination, or SBE), or a health care provider checking a woman's breasts for lumps (clinical breast examination, or CBE). These two types of screening are both important in the detection of changes in the breast that may be cancer. By examining her breasts once a month, a woman is likely to become very familiar with her breast contours, increasing the likelihood that she could detect a lump or other change in her breast. Health care providers are specially trained in breast examination and may be able to detect changes or lumps that cannot be felt by the woman herself.

- Who should have breast examinations?

Beginning at age 40, every woman at average risk should examine her breasts once a month for any changes in the breast, such as lumps, asymmetry, and skin changes, and have her breasts examined by her health care provider once a year. Women with a BRCA1 or BRCA2 mutation should begin breast examination at age 25.

- What are the benefits of breast examination?

Breast examination can detect lumps and other changes that may turn out to be early breast cancer. By finding cancer early it may be more easily treated and more likely to be cured. Because most studies of breast cancer screening have studied the combined effect of breast examination and mammography, it is hard to be sure exactly how much breast examination alone reduces a woman's chance of dying from breast cancer. However, most experts believe that self breast examination and clinical breast examination are important parts of breast cancer screening.

- What are the disadvantages of breast examination?

Because it is a painless, simple screening method, there are few risks associated with this type of screening. However, most lumps or other problems found by women or physicians that require evaluation are not cancer. Thus, women may undergo tests and surgeries that may be frightening and do not directly lead to a reduction in the risk of dying of breast cancer.

Mammography

- What is it?

A mammogram is an x-ray of the breasts that detects abnormalities in the breast tissue.

- Who has mammography?

For women of average risk, it is recommended that women over 40 undergo mammography screening once a year. For women who have a BRCA mutation, it is recommended that annual mammography screening begin at age 25.

- What are the benefits of mammography?

A mammogram provides a picture of the breast that can show changes or abnormalities in the breast tissue. In some cases, this allows mammography to detect early breast cancer, before it causes any symptoms. If breast cancer is found early, it is more likely to be curable.

For women between the ages of 50 and 69, mammography reduces the chance of dying from breast cancer by as much as 30 to 50%.
For women between the ages of 40 and 49, mammography may

be slightly less effective in detecting early breast cancer because younger women generally have more dense breasts. However, even in this younger age group, mammography appears to reduce the risk of dying from breast cancer by almost 25%. Furthermore, the benefits of mammography may be even greater in women at increased risk of breast cancer, such as women with a BRCA1 or BRCA2 mutation.

- What are the disadvantages of mammography?

There is some concern that beginning mammography screening between the ages of 25 and 35 could slightly increase a woman's risk for developing breast cancer from repeated exposure to radiation. Although this is a concern to be taken into account, the risk of radiation exposure through mammograms is very small. The benefits of early detection of breast cancer in a high risk woman greatly outweigh the possible risk of minimal radiation exposure.

As with breast examination, most abnormalities seen on a mammogram turn out not to be breast cancer at all. While it is always a relief to find out an abnormality is not cancer, having to undergo an evaluation can be unpleasant and cause some anxiety. This necessary evaluation of abnormal mammograms also leads to breast biopsies and other tests that may not have happened if the mammogram had not been done.

MRI

- What is it?

Breast MRI (Magnetic Resonance Imaging) uses the interaction between magnets and radio waves to produce cross-sectional pictures of the breast that are much more detailed than mammography. Its usefulness in screening women at high risk for breast cancer is currently under study.

- Who has breast MRI?

Breast MRI is not currently recommended as routine breast cancer screening for any group of women. However, women who are at high risk for breast cancer may be eligible to participate in research studies of breast MRI. Women who are pregnant, or have a pacemaker or any surgically implanted metal device, are not eligible for an MRI.

- What are the benefits of breast MRI?

Breast MRI gives a more detailed picture of the breast than a mammogram. This more detailed picture allows MRI to detect some early breast cancers that are not found by mammography. This technique is currently being investigated as a screening tool for high risk women.

- What are the disadvantages of breast MRI?

Breast MRI does not have any major side effects. Because the imaging requires that the woman lie completely still during the thirty to forty minute process, it can be a slightly uncomfortable experience, especially if a woman is claustrophobic. Breast MRI may also detect abnormalities that are not cancer – leading to breast biopsies and other tests that may not have happened if the MRI had not been done. The balance between the risk of these biopsies and the ability of the MRI to find early cancer is not yet known.

OVARIAN CANCER SCREENING:

Pelvic Examination

- What is a pelvic examination?

A pelvic exam involves a health care provider examining a woman's cervix, uterus and ovaries with an internal exam. It usually involves two parts: (1) a speculum examination where samples are taken from the cervix; and (2) bimanual examination where the uterus and ovaries are felt with a hand in the vagina. Because the ovaries can be felt at the time of a bimanual examination, a pelvic examination is sometimes considered one part of ovarian cancer screening.

- Who has a pelvic exam?

Any woman over the age of 18 or who is sexually active should have a pelvic exam once a year.

- What are the benefits of a pelvic exam?

A pelvic exam may detect changes in the ovaries that may represent early ovarian cancer. If ovarian cancers are found early, they may be more

easily treated and more likely to be cured. However, because the ovaries are difficult to feel, pelvic examination misses many early ovarian cancers. Currently, there are no studies that suggest that routine pelvic examinations will decrease a woman's risk of dying from ovarian cancer. However, PAP smears, which are done at the time of the speculum examination, are very important in reducing a woman's risk of dying from cervical cancer. Thus, it is reasonable to recommend annual pelvic examinations for all women.

- What are the disadvantages of this screening?

There are no major side effects to this type of screening. The major disadvantage to this screening is that it is not a very effective way to detect ovarian cancer, and some women find the procedure embarrassing or uncomfortable.

CA-125 and Trans-Vaginal Ultrasound of the Ovaries

- What are they?

These are tests that are often conducted together in order to detect early ovarian cancer in high-risk women. The CA-125 test is a blood test that measures the levels of a protein made by some ovarian cancers. A vaginal ultrasound produces pictures of the ovaries by inserting a small ultrasound probe into the vagina.

- Who has this screening?

Women who are at an increased risk for ovarian cancer, such as women with a BRCA1 or BRCA2 mutation, may begin to get an annual or biannual CA-125 test and ultrasound as early as age 25.

- What are the benefits of this screening?

CA-125 is present in low levels in the body at all times, but can become elevated with reproductive system cancers, such as ovarian cancer. Because the CA-125 test may detect the presence of ovarian cancer before a woman experiences any symptoms, CA-125 screening may catch ovarian cancer at an earlier stage when it is more likely to be curable.

By producing images of the ovaries, vaginal ultrasound may detect early ovarian cancer. Experts believe the tests in combination are better at detecting ovarian cancer than either test alone. Although there currently is no data showing that CA-125 test and vaginal ultrasound will reduce the chance of dying from ovarian cancer, the tests are relatively simple and painless. Thus, many women at high risk for developing ovarian cancer may wish to undergo these tests even in the absence of proven benefit if they are not yet ready to consider surgical removal of the ovaries.

- What are the disadvantages of this screening?

A CA-125 test does not test exclusively for ovarian cancer. An elevated CA-125 level may indicate a number of conditions, including menstruation, pregnancy, and ovarian cysts. Furthermore, CA-125 levels do not always rise in the early stages of ovarian cancer, meaning a woman may have early stage ovarian cancer and a normal CA-125 level. Vaginal ultrasound may also miss early ovarian cancers and detect many abnormalities that do not turn out to be cancer. Because these tests frequently miss early ovarian cancers, it is not clear that they will significantly reduce a woman's risk of dying of ovarian cancer. Because these tests may pick up abnormalities that are not ovarian cancer, women may undergo extra tests and even surgeries to evaluate these abnormalities. These extra tests can be unpleasant and anxiety producing and probably would not have been needed if the screening tests had not been done.

II. RISK REDUCING SURGERY

Prophylactic surgery involves the removal of healthy tissue, such as the breasts or ovaries, in order to decrease the risk of developing cancer.

Prophylactic Oophorectomy

- What is a prophylactic oophorectomy?

Prophylactic oophorectomy is the surgical removal of both ovaries before there is any sign of ovarian cancer to decrease the chance of developing ovarian cancer.

- How is a prophylactic oophorectomy performed?

A prophylactic oophorectomy is an operation that often can be performed through a laparascope (a thin, pencil-like instrument). If the oophorectomy is done with a laparascope, it usually does not require a hospital stay. Pre-operative tests are conducted on an outpatient basis. After not eating or drinking anything for several hours, a woman is given general anesthesia. During this time, she is asleep and cannot feel pain. A gas is pumped into the abdomen to give the surgeon space to operate safely. The laparoscope is inserted into the abdomen through a small incision just below the navel through which the ovaries are removed. Most women go home the same day as the operation. After a few days of mild abdominal discomfort, most women return to their normal activities, and are fully recovered in less than two weeks.

Occasionally a prophylactic oophorectomy will require an open surgery, especially if the uterus is removed at the same time (hysterectomy) or if a woman has had previous abdominal surgery. Therefore, a consultation with a gynecological oncologist is recommended. If an open surgery is necessary, the woman will stay in the hospital for several days after the surgery and will recover fully in four to six weeks.

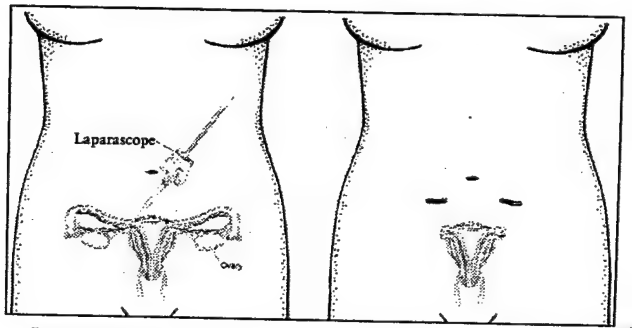
- What are the benefits of a prophylactic oophorectomy?

At present, there is only preliminary information about how much prophylactic oophorectomy reduces the risk of cancer in women with a BRCA1 or BRCA2 mutation. However, this preliminary information suggests prophylactic oophorectomy can reduce the chance of developing ovarian cancer by as much as 90%. In addition, it appears that removing the ovaries before menopause also reduces breast cancer risk by as much as 50-60%. However, a prophylactic oophorectomy does not guarantee that ovarian and/or breast cancer will not develop.

Some women may decide to have their uterus removed (hysterectomy) at the time they undergo prophylactic ooperectomy. Having a hysterectomy prevents development of endometrial cancer (cancer of the uterus) in the future. This issue may be particularly relevant to women who are considering tamoxifen for breast cancer risk reduction, as tamoxifen is known to increase the risk of endometrial cancer. However, having a hysterectomy at the time of oophorectomy requires a more extensive surgery, including the need for in-patient hospitalization and the small possibility of complications.

- What are the disadvantages of having a prophylactic oophorectomy?

Because the ovaries are totally removed, if a woman has not already experienced menopause, she will stop making estrogen and will undergo menopause, which may include some side effects. These may include hot flashes, mood changes, depression, fatigue/insomnia, and difficulty concentrating, among other symptoms. In most women these symptoms improve or disappear over a period of months. Removing ovaries in a post-menopausal woman will have no impact on menopausal symptoms because her ovaries have already stopped making estrogen. If a pre-menopausal woman has a prophylactic oophorectomy, she may choose to take hormone replacement therapy to ease the symptoms that occur after this surgery and to protect her heart and bones. In addition, because both ovaries are removed, pregnancy is not possible. Also, as with any surgical procedure, there is the risk associated with having surgery, which may lead to infections or other complications.



Laparascopic Surgery Post Oophorectomy

Prophylactic Mastectomy

• What is a prophylactic mastectomy?

Prophylactic mastectomy is the removal of one or both breasts before there is any sign of breast cancer in order to decrease the chance of developing breast cancer. There are two types of prophylactic mastectomies: total and subcutaneous. A total mastectomy, also known as a simple mastectomy, removes the skin, nipple, and breast tissue. A subcutaneous mastectomy removes breast tissue, but leaves the overlying skin and nipple. A subcutaneous mastectomy leaves more breast tissue behind than a total mastectomy. Because leaving more breast tissue behind may be associated with a higher risk of developing breast cancer, many experts recommend total mastectomies for women with BRCA1 or BRCA2 mutations who choose to undergo prophylactic mastectomy.

• How is a prophylactic mastectomy performed?

A prophylactic mastectomy is an operation that requires a short stay in the hospital. Once preoperative tests are completed as an outpatient and the surgery is scheduled, a woman checks into the hospital. At the time of the surgery, she is put under general anesthesia. During this time, she is asleep and cannot feel pain while the surgeon removes both breasts. Reconstructive surgery can be done at this time. Once the surgery is completed, the woman remains in the hospital for several days to recover, with additional time if reconstructive surgery has been done. Bandages and drains must be maintained for several weeks until the area heals. Careful follow-up is needed to prevent any infection.

• What are the benefits of a prophylactic mastectomy?

Prophylactic mastectomy decreases the risk of developing breast cancer, although how much it decreases the risk in women with BRCA1 or BRCA2 mutations is unknown. The largest study with carefully collected information suggests a reduction of up to 90% in women with a strong family history of breast cancer. While this is a significant reduction, it does not gaurantee that breast cancer will not develop.

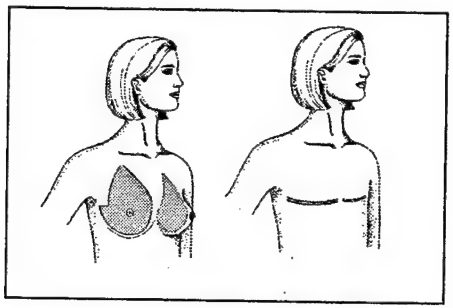
• Can breast reconstruction be done after prophylactic mastectomy?

Breast reconstruction is a surgical procedure that attempts to restore the shape of the breasts that have been removed. Reconstruction can be done at the time of the mastectomy or at a later date. When deciding about prophylactic mastectomy, it is important to recognize that reconstruction is not perfect, and may involve some complications.

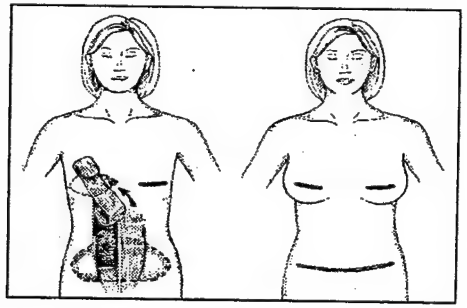
If a woman wishes to have reconstruction, there are several methods that can be used, although she may not be eligible for all of them. The first is a saline implant, which is placed under the muscle to replace the breast tissue that has been removed. Another option is to have a TRAM-flap, which involves moving of part of the abdominal (stomach) muscle and overlaying skin, and placing it on the chest in place of the breast tissue. Occasionally, a muscle from the back can be moved to replace the breast tissue. A plastic surgeon will evaluate each woman and suggest the possible reconstruction options and work with her to help her make a decision about reconstruction that is best for her.

• What are the disadvantages of a prophylactic mastectomy?

Aside from the cosmetic loss of the breasts, which can be partially corrected with reconstruction, the woman will lose sensation in the breast. This is because the nerves are cut around the breast during surgery. She will also lose the ability to breast feed due to the loss of the mammary glands, which produce milk.



Simple Bilateral Mastectomy



TRAM-flap Reconstruction

III. CHEMOPREVENTION

Chemoprevention, a new and growing field, involves taking a medicine to lower cancer risk. Currently, tamoxifen is the only medicine that has been approved by the Food and Drug Administration to reduce the risk of breast cancer. Oral contraceptives are not approved to reduce ovarian cancer risk, but several studies suggest they may be effective for this purpose.

Tamoxifen

- What is it?

Tamoxifen, trade name Novaldex®, is a pill, taken once a day, which has been used to treat breast cancer for over 20 years. In the breast it acts as an "anti-estrogen" to block the action of estrogen. Recently, a large study showed that taking tamoxifen for five years lowers the occurrence of breast cancer in women who are at increased risk. Taking tamoxifen for longer than five years was not evaluated in this study, and the optimal length of time to take tamoxifen to reducing the risk of breast cancer has not been established.

- Who can take tamoxifen?

Women who have already had breast cancer often take tamoxifen to reduce the risk of recurrence. Now, women who are at increased risk of breast cancer because of a family history, age, or other risk factors are eligible to take tamoxifen to reduce the risk of first breast cancers. Although there has not been a specific study of tamoxifen in women with a BRCA1 or BRCA2 mutation, a woman with a BRCA1 or BRCA2 mutation is eligible because having this mutation is considered being at high risk.

- What are the benefits of taking tamoxifen?

One study suggests that tamoxifen reduces the risk of developing breast cancer by approximately 50%. Other studies have suggested that tamoxifen may also lower cholesterol levels and improve bone density. These effects may make women on tamoxifen less likely to have a heart attack and a bone fracture because of osteoporosis, the weakening of bones, although more studies need to be done.

- What are the disadvantages to taking tamoxifen?

Women who are over 50 are at the greatest risk of experiencing side effects from tamoxifen. Tamoxifen increases the rate of cancer of the uterus (endometrial cancer) slightly in women who have not had a hysterectomy. However, the risk is small, and this cancer is usually easily curable. Tamoxifen also increases the rate of blood clots, including clots in the lung (pulmonary embolism) and clots in major veins (deep vein thrombosis), and cataracts. Tamoxifen also may cause symptoms of menopause in women who have not yet undergone menopause, such as hot flashes, mood changes, insomnia, and vaginal dryness or discharge. However, tamoxifen does not cause menopause, and it is still possible to have children once the tamoxifen is stopped.

Oral Contraceptives

- What are they?

Oral contraceptives (birth control pills) are pills that are taken daily to prevent pregnancy. They generally contain low doses of estrogen and progesterone. These pills are also thought to lower the risk of ovarian cancer.

- Who can take oral contraceptives?

Women usually take oral contraceptives as birth control. Because of studies suggesting oral contraceptives reduce the risk of ovarian cancer, women who are at increased risk of ovarian cancer and have not yet experienced menopause may consider taking oral contraceptives to lower their ovarian cancer risk. Women with a BRCA1 or BRCA2 mutation may take oral contraceptives because of their increased risk of ovarian cancer.

- What are the benefits of taking oral contraceptives?

Several studies suggest that women who take oral contraceptives prior to menopause have about half the risk of developing ovarian cancer later in life as women who do not take oral contraceptives. In addition, oral contraceptives prevent pregnancy and may improve some premenstrual symptoms, such as acne, mood swings, and uterine cramping.

- What are the disadvantages to taking oral contraceptives?

Side effects of oral contraceptives include blood clots, including clots in the lung (pulmonary embolism), high blood pressure, stroke, nausea, headaches and weight gain in some women. Women who smoke cigarettes are at particular risk for developing blood clots and strokes. Some studies suggest early types of oral contraceptives may slightly increase the risk of breast cancer. However, new types of oral contraceptives have lower doses of estrogen and are unlikely to significantly increase breast cancer risk.

IV. Hormone Replacement Therapy and Its Alternatives

At the time of menopause, a woman's ovaries stop producing estrogen and progesterone. Decreased levels of these hormones have many effects, including menopausal symptoms (such as hot flashes and mood swings), decreased bone density and increased cholesterol levels. After menopause, a woman's risk of osteoporosis and heart disease increases significantly. Several strategies have been proposed to help women manage the changes that occur with menopause, including use of hormone replacement therapy and other medications. Because these therapies have many effects that may compete with each other, deciding how best to manage the effects of menopause can be particularly difficult for women with BRCA1 or BRCA2 mutations.

Hormone Replacement Therapy

- What is hormone replacement therapy?

Hormone replacement therapy (HRT) contains estrogen or estrogen and progesterone, like a birth control pill. It is a pill that is taken once a day every day, or a patch that is worn on the skin like a Band-Aid. HRT is commonly used in women who have reached menopause to replace the female hormones that a woman's body no longer produces. All women on HRT receive estrogen, and women who have not had their uterus removed also receive progesterone. HRT is a consideration for women with BRCA1 or BRCA2 mutations if they choose to have a prophylactic oophorectomy before undergoing menopause, or when they experience menopause through natural aging.

- Who can take HRT?

Women who are undergoing or have completed natural menopause or women who have had their ovaries removed before they underwent natural menopause may consider taking HRT. If a woman has a personal history of breast cancer, most experts will not recommend HRT.

- What are the benefits of HRT?

HRT alleviates many of the symptoms of menopause such as hot flashes, sweats, mood changes, and disturbed sleep. HRT also decreases a

woman's chance of developing coronary heart disease and osteoporosis by as much as 50%. HRT may also improve memory and reduce the risk of colon cancer. Overall, HRT has been shown to significantly prolong life in women at average risk of breast cancer.

Women may use HRT for their lifetime or for shorter periods of time following menopause. Many premenopausal woman who undergo prophylactic oophorectomy may choose to take HRT until about age 50 (the time of natural menopause) to alleviate the menopausal symptoms that develop because of the oophorectomy.

- What are the risks and disadvantages of taking HRT?

HRT, if taken after natural menopause, may slightly increase a woman's chance of developing breast cancer. The effect of HRT on the risk of breast cancer in women with BRCA1 or BRCA2 mutations is not currently known. Furthermore, the specific effects of HRT on breast cancer risk remain controversial.

Estrogen therapy without progestin may also increase the rate of cancer of the uterus. HRT may also increase the rate of blood clots. Less serious side effects include headaches, nausea, fluid retention, swollen breasts, weight gain, and vaginal discharge.

Raloxifene

- What is it?

Raloxifene (trade name Evista®) is a drug that has been recently shown to prevent osteoporosis (the weakening of bones) in postmenopausal women. Raloxifene is a Selective Estrogen Receptor Modulator (SERM) that acts as estrogen on the heart and bones but like an anti-estrogen on the breast and uterus. Raloxifene is a pill that is taken daily.

- Who can take raloxifene?

Raloxifene is an alternative to HRT in post-menopausal women concerned about osteoporosis. It is especially attractive to women who are at an increased risk for breast cancer, as it does not increase breast cancer risk, and may actually decrease breast cancer risk.

- What are the benefits of taking raloxifene?

As a SERM, raloxifene has positive estrogen-like effects on bone density and cholesterol levels. It has been shown to prevent the development of osteoporosis and decrease LDL ("bad") cholesterol levels in post-menopausal women. These effects may result in a decrease of bone fractures and heart disease, although more studies need to be done. Because raloxifene blocks the action of estrogen on the breasts and uterus, it would be unlikely to increase the risk for breast or endometrial cancers. In fact, preliminary data suggest that raloxifene does not increase uterine cancer risk and may decrease the incidence of breast cancer in post-menopausal women. Current studies are evaluating the effect of raloxifene on breast cancer risk.

It is important to recognize that raloxifene does not provide relief from menopausal symptoms such as hot flashes, mood swings, etc. that can be provided by HRT.

- What are the disadvantages of taking raloxifene?

Because raloxifene is a relatively new drug, we do not yet know all of its side effects. However, in the trials so far, raloxifene, like tamoxifen and HRT, has increased the rate of blood clots. Raloxifene may also cause hot flashes and leg cramps. Unlike tamoxifen, raloxifene does not appear to increase the risk of endometrial cancer.

V. LIFESTYLE CHANGES

Some women who find out they have a mutation in BRCA1 or BRCA2 ask about lifestyle changes they can make to reduce their risk of cancer. Although there have been many studies of lifestyle and cancer risk, there are no specific indications that lifestyle changes can lower the risk of breast or ovarian cancer. Thus, it is difficult to make specific recommendations about lifestyle changes for women with BRCA1 or BRCA2 mutations. The following information is provided to help you understand what is known about the effects of lifestyle on the risk of breast and ovarian cancer.

• Alcohol

Several studies have found that women who have more than three drinks a day have an increased risk of breast cancer. A "drink" is considered a glass of wine, a bottle of beer or one shot of hard liquor. While no study has shown that cutting back on alcohol intake can lower a woman's risk of breast cancer, it is reasonable to keep alcohol intake to less than three drinks a day.

• Diet

The effect of dietary fat on the risk of breast cancer has been studied many times with mixed results. Some studies have found that high fat diets increase the risk of breast cancer, while others have found no association. Again, while no study has shown that decreasing dietary fat can lower a woman's risk of breast cancer, it is reasonable to keep dietary fat below the recommended 30% of total caloric intake.

Vitamins and dietary supplements have received a lot of attention as possible cancer risk reduction treatments. Because there are no trials that support the benefit of supplements in reducing cancer risk, specific supplements are not recommended at this time. While the decision about taking any of these supplements is highly individual, it is important to remember that the risks of many of these supplements are not yet known either. Many claims about protecting against cancer are exaggerated or not true. Some supplements may even be harmful.

Dietary supplements that have been publicized as preventing cancer include the following supplements:

Antioxidants are thought to combine with free radicals, which may cause cancer by damaging the DNA in cells, to reduce their ability to do damage. Vitamins A, C, and E, which are found in fruits and vegetables, are antioxidants.

Selenium is a nutrient found in food that has been shown in a few studies to be associated with a lowered incidence of breast cancer.

Genistein, which is found in soy products such as tofu, is a phytoestrogen, or weak plant estrogen. This compound may block the action of stronger estrogens in the breast, possibly lowering the risk of developing breast cancer.

Countless other foods, ranging from flaxseed to mushroom tea, have been proposed as having cancer fighting properties. While many important medicines have come from plant sources, none of these foods have yet been proven to reduce cancer risk. Importantly, by eating a well-balanced and healthy diet, most of the natural cancer fighting agents are automatically included. The National Cancer Institute recommends eating at least five fruits and vegetables every day to reduce the risk of developing cancer.

• Exercise

Several studies have found that women who perform aerobic exercise for at least four hours a week have a lower risk of breast cancer than women who do not exercise. While no study has shown that becoming more active will specifically reduce the risk of developing breast cancer, in general, exercise has been shown to be beneficial to health and may also decrease the risk of breast cancer.

In the end, it is important to have a healthy diet and exercise, regardless of a woman's risk for breast and ovarian cancer. The American Cancer Society has issued guidelines promoting a balanced diet that is low in fat, high in fiber, and includes plenty of fruits and vegetables. These recommendations can be found on-line at www.cancer.org, under the subheading prevention, or from your physician. These are useful to any woman interested in improving her health, regardless of risk for breast and ovarian cancer.

VI. OTHER IMPLICATIONS OF HAVING A BRCA MUTATION

• Implications for family

If a woman or man tests positive for either a BRCA1 or BRCA2 mutation, his/her children have a 50% chance of also having the BRCA1 or BRCA 2 mutation, regardless of whether they are male or female. Other first-degree relatives such as brothers and sisters also have a 50% chance of carrying the mutation. Less closely related blood relatives may have lower chances of carrying a mutated BRCA1 or BRCA2 gene.

Genetic testing is a personal decision, but learning about the presence of an inherited mutation that increases risk for cancer can also affect other family members, and possibly even family relationships. Other relatives could learn about their cancer risk through testing a parent, brother, sister or cousin, for example, and this information may or may not be welcome. Once a mutation has previously been identified in a family, testing other family members is technically simpler, less expensive, and highly informative. While we strongly encourage people to share genetic testing information with relatives, ultimately each family member should choose for him or herself whether or not to be tested.

• Implications for Health Insurance

Some individuals who learn they have a BRCA1 or BRCA2 mutation are concerned about the possibility of genetic discrimination in health or life insurance. Although many activists, including representatives from the University of Pennsylvania, are working with groups to support protection from the possibility of genetic discrimination, discrimination has never been associated with genetic testing for BRCA1 or BRCA2 mutations. Furthermore, individuals who have been diagnosed with cancer in the past are not thought to be at any increased risk of discrimination based on genetic testing.

Most Americans get their medical insurance through their employer, and as part of a group. Even people who have their own businesses often join with a group to buy into a medical insurance plan. People who have health insurance through a group are insured with others at the same

rate. A group health plan can offer any type of available insurance, such as Blue Cross/ Blue Shield, HMO insurance, or contract with any plan it chooses. A federal law enacted in 1997 (the Health Insurance Portability and Accountability Act, or HIPAA) makes it illegal to single someone out in a group health plan for higher or lower payments for their medical insurance. The same federal law makes it illegal to drop a person, exclude someone, or deny any medical treatment, including for cancer, by saying the person has a pre-existing condition.

The HIPAA law applies as long as a person maintains continuous group health insurance coverage with the same, or with a new group health insurance plan. Therefore, people who change jobs do not need to fear being denied access to the new group health plan policy. The policy can be through an employer, or any group, such as a trade group, or retired persons group such as AARP.

People who have group insurance are usually not underwritten. Underwriting is the process in which an insurance company tries to determine what a person may actually cost to insure. People are underwritten for car insurance when they are asked how many accidents they have had, their age, their gender, and where they live. Each of these things can affect their insurance rates. Underwriting for health insurance may include questions about weight, smoking, and the presence of significant medical conditions like heart disease or cancer. If a person signed up for medical insurance without filling out a detailed medical questionnaire, then he/she was not underwritten. And, if he/she was not underwritten, then past medical history, including risk of cancer or genetic testing, will not be considered when setting the rate he/she pays for medical insurance. People with government-sponsored insurance, such as Medicare and Medicaid, or most group insurance are not underwritten.

A small number of Americans purchase their own individual health insurance, outside a group and are underwritten. They are not protected through the same federal law that protects those in group health plans. However, there are many states that have individually enacted laws to prevent genetic discrimination, whether a person is in a group or private plan (in 1999, New Jersey had a comprehensive protection law, and Delaware

and Pennsylvania had no laws). There are also limits to state laws that will vary depending on the state and legislation. There are only a handful of documented cases of genetic discrimination in this country, none of which were associated with cancer, thus, people assume their personal risks are much higher than they are.

- Implications for Life Insurance

Individuals who purchase life insurance through their employers and are not underwritten are unlikely to experience changes in life insurance coverage because of genetic testing. For people who are underwritten for life insurance, a personal or family history of cancer, with or without genetic testing, could affect life insurance rates. Although most life insurance companies do not ask about genetic testing, this may change in the future. Some people choose to purchase life insurance before undergoing genetic testing. Legislative and policy efforts are currently trying to decide whether life insurance companies should have access to genetic test results.

- Implications for Employment

Employment discrimination occurs if an employer singles people out with any medical condition that may affect how much an employee could cost a company. For example, an employer may believe that a person with a prior history of cancer is at risk of being absent more, and choose to promote someone else over this person, even if they are similarly qualified. For this reason, we suggest not discussing medical information, including information about genetic testing, in the workplace. It is hard to know how common employment discrimination is, since it is rarely reported.

- Implications of Sharing Results

There are two ways of being tested and receiving results; through clinical testing and through research testing. Clinical testing is a process that involves your results being placed in your medical records, which are accessible to doctors and health insurance companies.

Research results from genetic testing are considered confidential, and do not have to be placed in a medical record. Some people who underwent research testing wonder whether or not they should share this information with their doctors and other health care providers, since then the information will likely be placed in a medical chart. This is a personal decision, and the choice may be affected by the personal situation, as previously described.

There may be substantial benefits to sharing information about the presence of a gene mutation with doctors, since they are partners in delivering the most appropriate, personalized health care to their patients. A woman may be facing some difficult decisions, such as whether or not to take hormone replacement therapy, or have prophylactic surgery, that she might want to discuss with her personal doctors. In addition, as the field of cancer genetics advances, doctors may be able to alert their patients to new interventions that may be tailored to those with genetic risk.

In addition, women often choose to inform their insurance companies to get coverage for genetic testing, preventive surgery, or other management options, since paying out of pocket can become a considerable expense.

Booklet Update

Since the publication of Health Care Options for Women at Risk for Breast and Ovarian Cancer in 2000, scientist continue to learn more about BRCA1 and BRCA2 mutations. In order to provide you with the most recent information we have added this supplement to the booklet.

The information in this booklet was designed to help women with a BRCA 1 or 2 mutation make decisions about managing future cancer risk. For women with a current diagnosis of breast cancer, this information may not be directly relevant to their decisions about current cancer treatment. For example the role of tamoxifen for breast cancer prevention is different from the role of tamoxifen for breast cancer treatment, and these differences should be discussed with your doctor.

Recent data from a randomized control trial among healthy, postmenopausal women with a uterus showed that hormone replacement, with estrogen and progestin, slightly increases the risk of coronary disease and breast cancer, and decreases the risk of bone fractures. The use of hormone replacement therapy (HRT) in women with a uterus is no longer thought to increase overall life expectancy.

Recent findings from a study about oral contraceptives and breast cancer risk has shown that current and former oral contraceptive use among women 35-64 years of age does not increase the risk of breast cancer. One smaller study suggests that use of oral contraceptives before age 30, for 5 or more years, or before 1975 slightly increases the risk of breast cancer in women with BRCA1 mutations but not in women with BRCA2 mutations.

Even at the time of this update, the medical community continues to learn more about BRCA1 and BRCA2 mutations, and new options for managing cancer risk may become available at anytime. Regular contact with health care providers can keep women with BRCA 1 or BRCA2 mutation up to date of new information.

Appendix B

Introduction to study letter

Study packet cover letter

UNIVERSITY OF
PENNSYLVANIA
HEALTH SYSTEM

Katrina Armstrong, M.D.
Assistant Professor of Medicine

Department of Medicine
Division of General Internal Medicine

Dear Ms. XX,

We are currently conducting a study at the Cancer Risk Evaluation Program that we believe you may be interested in participating. This study, "Decision Aid for Women Navigating Cancer Risk," aims to improve the information that women with either a BRCA1 or BRCA2 mutation receive about their risk management options. Because managing your risk is a complex decision, involving complicated information, we are constantly searching for new and better ways to help women with a BRCA mutation understand their options for cancer risk management. By participating in this study, you will receive extra information to help you manage your risk of developing breast or ovarian cancer. Participating in this study will not affect your eligibility for studies involving new cancer risk management options.

We will contact you within the next two weeks to answer any questions you may have about this study and to see if you are interested in participating. Please feel free to contact the research coordinator, Nikki, at 215-573-7907 if you would like to learn more about the study sooner. If you agree to participate we will send you additional material for review covering the options available to women of your status. If you choose not to participate, your health care will in no way be compromised, as this is a voluntary study. We look forward to speaking with you in the near future.

Sincerely,

Katrina Armstrong, MD

Barbara Weber, MD

Nikki Peters
Research Coordinator

1233 Blockley Hall • 423 Guardian Drive • Philadelphia, PA 19104-6021 • Office: (215) 898-0957 • Fax: (215) 573-8778 • karmstro@mail.med.upenn.edu

UNIVERSITY OF
PENNSYLVANIA
HEALTH SYSTEM

Katrina Armstrong, M.D.
Assistant Professor of Medicine

Department of Medicine
Division of General Internal Medicine

Dear Ms. XX,

Thank you for your interest to participate in the "Decision Aid for Women Navigating Cancer Risk" study. This study aims to improve the information that women with either a BRCA1 or BRCA2 mutation receive about their risk management options. Because managing your risk is a complex decision, involving complicated information, we are constantly searching for new and better ways to help women with a BRCA mutation understand their options for cancer risk management. By participating in this study, you will receive extra information to help you manage your risk of developing breast or ovarian cancer. Participating in this study will not affect your eligibility for studies involving new cancer risk management options.

Enclosed you will find the "Assessment of Risk Factors & Interest in Risk Reduction Options Questionnaire", the "Health Care Options for Women at Risk for Breast and Ovarian Cancer" booklet, and a consent form. Please complete this questionnaire and send it back to us in the self-address envelope that has been provided. The booklet is for you to keep. The consent form describes in detail the study and what your participation will involve. Please review and bring the booklet and unsigned consent form with you to the counseling session.

Upon receiving the completed questionnaire we will contact you to set up a time to meet with the research counselor. If you have any questions before then please feel free to call Nikki Peters at 215-573-7907. Thank you again for your interest.

Sincerely,

Katrina Armstrong, MD

Barbara Weber, MD

Nikki Peters
Research Coordinator

1233 Blockley Hall • 423 Guardian Drive • Philadelphia, PA 19104-6021 • Office: (215) 898-0957 • Fax: (215) 573-8778 • karmstro@mail.med.upenn.edu

Appendix C

Assessment of Risk Factors & Interest in Risk Reduction Options questionnaire

Decision Aid for Women Navigating Cancer Study baseline questionnaire

Decision Aid for Women Navigating Cancer Study follow-up questionnaire

Decision Aid for Women Navigating Cancer Study (DAWN)

Assessment of Risk Factors & Interest in Risk Reduction Options

Please answer the following questions about your personal medical history as well as your interest in risk reduction options. Thank you.

1. Name_____

   Daytime Phone Number _____

   Age_____

2. Do you have high blood pressure? ☐ Yes ☐ No ☐ Not sure

   What was your most recent blood pressure reading (if known)? _____

   Do you take medication for high blood pressure? ☐ Yes ☐ No ☐ Not sure

3. Do you have diabetes? ☐ Yes ☐ No ☐ Not sure

4. Do you have high cholesterol? ☐ Yes ☐ No ☐ Not sure

   What was your most recent cholesterol reading (if known)? Total: _____

   LDL ("bad cholesterol"): _____

   HDL ("good cholesterol"):_____

   Do you take medication for high cholesterol? ☐ Yes ☐ No ☐ Not sure

5. Do you smoke cigarettes? ☐ Yes ☐ No ☐ Not sure

   If yes: How many cigarettes do you smoke a day? _____

6. Have you ever had a heart attack? ☐ Yes ☐ No ☐ Not sure

   Have you ever had angina? ☐ Yes ☐ No ☐ Not sure

   Do you take medication for heart disease? ☐ Yes ☐ No ☐ Not sure

7. Have you ever had breast cancer? ☐ Yes ☐ No ☐ Not sure

   If yes, was it node positive or node negative?

   ☐ Node positive ☐ Node negative ☐ Not sure

8. Have you ever had ovarian cancer? ☐ Yes ☐ No ☐ Not sure

9. Do you have osteoporosis? ☐ Yes ☐ No ☐ Not sure

Please answer the following questions about your interest in some options for managing your health by circling one number for each question below.

1. Are you interested in participating in clinical trials (research studies) of investigational cancer risk reducing treatments?

1	2	3	4	5
Not at all interested				Extremely interested

2. Are you interested in having a prophylactic mastectomy?

1	2	3	4	5
Not at all interested				Extremely interested

3. Are you interested in having a prophylactic oophorectomy?

1	2	3	4	5
Not at all interested				Extremely interested

4. Are you interested in taking tamoxifen (Nolvadex™) for cancer risk reduction?

1	2	3	4	5
Not at all interested				Extremely interested

5. Are you interested in taking hormone replacement therapy after menopause?

1	2	3	4	5
Not at all interested				Extremely interested

6. Are you interested in taking raloxifene (Evista™) after menopause?

1	2	3	4	5
Not at all interested				Extremely interested

Decision Aid for Women Navigating Cancer Study (DAWN)

Women found to have a BRCA1 or BRCA2 mutation are faced with many options for managing their risk of developing breast and/or ovarian cancer. These management options range from taking tamoxifen (Nolvadex™) to having a prophylactic mastectomy. In addition, women entering menopause may be faced with decisions about therapies such as hormone replacement therapy (HRT) or raloxifene (Evista™) that may also affect their risk of osteoporosis and heart disease.

Now, thinking about the choices that you may be facing, please look at the following comments other people have made. Please circle the number from 1 (strongly agree) to 5 (strongly disagree) that best shows how you feel about the decisions you are facing.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
These decisions are hard for me to make.	1	2	3	4	5
I'm unsure what to do in this situation.	1	2	3	4	5
It's clear which choices are best for me.	1	2	3	4	5
I'm aware of the management options I have to modify my risk.	1	2	3	4	5
I feel I know the benefits of the management options for my risk.	1	2	3	4	5
I am satisfied that I am adequately informed about the issues important to my decision.	1	2	3	4	5
I feel I know the risks and side effects of the management options for my risk.	1	2	3	4	5
I have the right amount of support from others in my decision making process.	1	2	3	4	5
I feel I am making an informed choice.	1	2	3	4	5
My decision shows what is most important for me.	1	2	3	4	5
I expect to stick with my decision.	1	2	3	4	5
I am satisfied that these are my decisions to make.	1	2	3	4	5
I expect to successfully carry out the decisions that I am making.	1	2	3	4	5
I am satisfied that my decisions are consistent with my personal values.	1	2	3	4	5
The decisions that I am making are the best possible for me personally.	1	2	3	4	5

For the next set of items, please tell us whether you strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, or strongly agree.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
The important medical decisions should be made by your doctor, not by you.					
You should go along with your doctor's advice even if you disagree with it.					
When hospitalized, you should not be making decisions about your own care.					
You should feel free to make decisions about everyday medical problems.					
If you were sick, as your illness became worse, you would want your doctor to take greater control.					
You should decide how frequently you need a check up.					

Now suppose you developed a sore throat, stuffy nose, and cough that lasted for three days. You are about to call your doctor on the telephone. Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor, or the doctor alone?

	You alone	Mostly you	Doctor & you equally	Mostly doctor	Doctor alone
Whether you should be seen by a doctor.					
Whether a chest x-ray should be taken.					
Whether you should try taking cough syrup.					

Suppose you went to your doctor for a routine physical examination and he or she found that everything was all right except that your blood pressure was high (170/100). Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor, or the doctor alone?

	You alone	Mostly you	Doctor & you equally	Mostly doctor	Doctor alone
When the next visit to check your blood pressure should be.					
Whether you should take time off from work to relax.					
Whether you should be treated with medication or diet.					

Suppose you had an attack of severe chest pain that lasted for almost an hour, frightening you enough so that you went to the emergency room. In the emergency room the doctors discovered that you are having a heart attack. Your own doctor is called and you are taken up to the intensive care unit. Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor or the doctor alone?

	You alone	Mostly you	Doctor & you equally	Mostly doctor	Doctor alone
How often the nurses should wake you up to check your temperature and blood pressure.					
Whether you may have visitors aside from your immediate family.					
Whether a cardiologist should be consulted.					

For the next set of items, please tell us whether you strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, or strongly agree.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
As you become sicker you should be told everything about your illness.					
You should understand completely what is happening inside your body as a result of your illness.					
Even when news is bad, you should be well informed.					
Your doctor should explain the purpose of your laboratory tests.					
You should be given information only when you ask for it.					
It is important for you to know all the side effects of your medication.					
Information about your illness is as important as your treatment.					
When there is more than one method to treat a problem, you should be told about each one.					

Please check the appropriate box next to the statement about you during the past week:

	Rarely/none of the time (<1/ day)	Occasionally/ little of the time (1-2 days)	Some/ moderate amount of time (3-4 days)	Most/ all of the time (5-7 days)
I was bothered by things that don't usually bother me.				
I did not feel like eating; my appetite was poor.				
I felt that I could not shake the blues even with help from my family and friends.				
I felt that I was just as good as other people.				
I had trouble keeping my mind on what I was doing.				
I felt depressed.				
I felt that everything that I did was an effort.				
I felt hopeful about the future.				
I thought that my life had been a failure.				
I felt fearful.				
My sleep was restless				
I was happy.				
I talked less than usual.				
I felt lonely.				
People were unfriendly.				
I enjoyed life.				
I had crying spells.				
I felt sad.				
I felt that people dislike me.				
I could not get "going."				

The next questions ask about what you think about your risk of developing cancer or heart disease.

What do you believe is your chance of developing breast cancer by age 70 if you have yearly mammograms, but choose not to have prophylactic surgery, take tamoxifen, or take HRT (Hormone Replacement Therapy) or raloxifene after menopause?_____%

...How about if you do have a prophylactic mastectomy? _____%

...How about if you do have a prophylactic oophorectomy? _____%

...How about if you do take tamoxifen? _____%

...How about if you do take HRT after menopause? _____%

...How about if you do raloxifene after menopause? _____%

What do you believe your chance of developing ovarian cancer is by age 70 if you choose not to have a prophylactic oophorectomy? _____%

...How about if you do have a prophylactic oophorectomy? _____%

What do you believe your chance of developing heart disease by age 70 is if you choose not to take HRT or raloxifene at the onset of menopause? _____%

...How about if you do take HRT at the onset of menopause? _____%

...How about if you do take raloxifene at the onset of menopause? _____%

The next questions are about comments made by people concerned about breast cancer (BC), and/or ovarian cancer (OC). Please tell us how frequently these comments were true for you during the past week.

During the past week:	Not at all	Rarely	Sometimes	Often
You thought about BC and/or OC when you didn't mean to.				
You had trouble falling asleep or staying asleep because of pictures or thoughts about BC and/or OC that came into your mind.				
You had waves of strong feelings about BC and/or OC.				
You had dreams about BC and/or OC.				
Pictures about BC and/or OC popped into your mind.				
Any reminder brought back feelings about BC and/or OC.				

Please answer the following questions about some management options that you may have heard of.

Prophylactic Mastectomy (preventative removal of the breasts)

Have you had a prophylactic mastectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic mastectomy:

In the next month? ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the future? ☐ Yes ☐ No ☐ Not sure

Prophylactic Oophorectomy (preventative removal of the ovaries)

Have you had a prophylactic oophorectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic oophorectomy:

In the next month? ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the future? ☐ Yes ☐ No ☐ Not sure

Tamoxifen (Nolvadex™) for breast cancer prevention

Are you taking tamoxifen? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking tamoxifen:

In the next month ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the future? ☐ Yes ☐ No ☐ Not sure

Hormone Replacement Therapy (HRT) after menopause

Are you taking HRT? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking HRT:

In the next month? ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

At the time of menopause? ☐ Yes ☐ No ☐ Not sure

Raloxifene (Evista™) after menopause

Are you taking raloxifene? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking raloxifene:

In the next month?	☐ Yes	☐ No	☐ Not sure
In the next 6 months?	☐ Yes	☐ No	☐ Not sure
At the time of menopause?	☐ Yes	☐ No	☐ Not sure

Outcomes of Decision Aid for Women Navigating Cancer Study (DAWN)

As you know, women found to have a BRCA1 or BRCA2 mutation are faced with many options for managing their risk of developing breast and/or ovarian cancer. You have read and heard about many of your management options, now, thinking about the choices that you are making, please answer the following questions about some management options that are available to you.

Participating in Clinical Trials of Investigational Options for Managing Cancer Risk

1. Have you joined a research study of investigational treatments for reducing cancer risk (such as the STAR trial)? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about participating in a research study of new treatments:

☐ Yes ☐ No ☐ Not sure

Prophylactic Mastectomy (preventative removal of the breasts)

2a. Which of the following best describes your decision about prophylactic mastectomy:

☐ I never considered having a prophylactic mastectomy.

☐ I have decided against having a prophylactic mastectomy.

☐ I am considering having a prophylactic mastectomy.

☐ I am planning on having a prophylactic mastectomy at a later date.

☐ I have had or am scheduled to have a prophylactic mastectomy.

☐ Other: _____

2b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for a prophylactic mastectomy.

☐ Slightly in favor for a prophylactic mastectomy.

☐ Neither in favor for or against a prophylactic mastectomy.

☐ Slightly against a prophylactic mastectomy.

☐ Strongly against a prophylactic mastectomy.

Prophylactic Oophorectomy (preventative removal of ovaries)

3a. Which of the following best describes your decision about prophylactic oophorectomy:

☐ I never considered having a prophylactic oophorectomy.

☐ I have decided against having a prophylactic oophorectomy.

☐ I am considering having a prophylactic oophorectomy.

☐ I am planning on having a prophylactic oophorectomy at a later date.

☐ I have had or am scheduled to have a prophylactic oophorectomy.

☐ Other: _____

3b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for a prophylactic oophorectomy.

☐ Slightly in favor for a prophylactic oophorectomy.

☐ Neither in favor for or against a prophylactic oophorectomy.

☐ Slightly against a prophylactic oophorectomy.

☐ Strongly against a prophylactic oophorectomy.

Tamoxifen (Nolvadex™) for breast cancer prevention

4a. Which of the following best describes your decision about Tamoxifen:

☐ I never considered taking Tamoxifen.

☐ I have decided against taking Tamoxifen.

☐ I am currently considering taking Tamoxifen.

☐ I am planning on taking Tamoxifen at a later date.

☐ I am taking Tamoxifen.

☐ Other: _____

4b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for Tamoxifen.

☐ Slightly in favor for Tamoxifen.

☐ Neither in favor for or against Tamoxifen.

☐ Slightly against Tamoxifen.

☐ Strongly against Tamoxifen.

Hormone Replacement Therapy (HRT) after menopause

5a. Which of the following best describes your decision about Hormone Replacement Therapy (HRT):

☐ I never considered taking HRT.

☐ I have decided against taking HRT.

☐ I am currently considering taking HRT.

☐ I am planning on taking HRT at a later date.

☐ I am taking HRT.

☐ Other: _____

5b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for HRT.

☐ Slightly in favor for HRT.

☐ Neither in favor for or against HRT .

☐ Slightly against HRT.

☐ Strongly against HRT.

Raloxifene (Evista™) after menopause

6a. Which of the following best describes your decision about Raloxifene:

☐ I never considered taking Raloxifene.

☐ I have decided against taking Raloxifene.

☐ I am currently considering taking Raloxifene.

☐ I am planning on taking Raloxifene at a later date.

☐ I am taking Raloxifene.

☐ Other: _____

6b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for Raloxifene.

☐ Slightly in favor for Raloxifene.

☐ Neither in favor for or against Raloxifene.

☐ Slightly against Raloxifene.

☐ Strongly against Raloxifene.

7. Overall where do you feel you are in your decision making process?

☐ I have not thought about my options for managing my breast cancer risk.

☐ I have just begun to think about my options for managing my breast cancer risk.

☐ I am deciding on how to manage my breast cancer risk.

☐ I have decided how to manage my breast cancer risk.

8. Please tell me how many times you have thought about each statement during the past week:

Was it Rarely/None of the time, Occasionally, Somewhat, or most of the time?

	Rarely/none of the time (<1/ day)	Occasionally/ little of the time (1-2 days)	Some/ moderate amount of time (3-4 days)	Most/ all of the time (5-7 days)
a. I was bothered by things that don't usually bother me.				
b. I did not feel like eating; my appetite was poor.				
c. I felt that I could not shake the blues even with help from my family and friends.				
d. I felt that I was just as good as other people.				
e. I had trouble keeping my mind on what I was doing.				
f. I felt depressed.				
g. I felt that everything that I did was an effort.				
h. I felt hopeful about the future.				
i. I thought that my life had been a failure.				
j. I felt fearful.				
k. My sleep was restless				

l. I was happy.				
m. I talked less than usual.				
n. I felt lonely.				
o. People were unfriendly.				
p. I enjoyed life.				
q. I had crying spells.				
r. I felt sad.				
s. I felt that people dislike me.				
t. I could not get "going."				

The next questions ask about what you think about your risk of developing cancer or heart disease. Give me a percent between 0 and 100%.

9. What do you believe that your chance of developing breast cancer is by age 70 if you have yearly mammograms, but choose not to have prophylactic surgery, take tamoxifen, or take HRT (Hormone Replacement Therapy) or raloxifene after menopause in a percentage? _____ %

10. ...How about if you do have a prophylactic mastectomy? _____%

11. ...How about if you do have a prophylactic oophorectomy? _____%

12. ...How about if you do take tamoxifen? _____%

13. ...How about if you do take HRT after menopause? _____%

14. ...How about if you do raloxifene after menopause? _____%

15 .What do you believe your chance of developing ovarian cancer is by age 70 if you choose not to have a prophylactic oophorectomy in a percentage? _____ _____%

16. ...How about if you do have a prophylactic oophorectomy? _____%

17. What do you believe your chance of developing heart disease by age 70 is if you choose not to take HRT or raloxifene at the onset of menopause in a percentage? _____%

18. ...How about if you do take HRT at the onset of menopause? _____%

19. ...How about if you do take raloxifene at the onset of menopause? _____%

20.The next questions are about comments made by people concerned about breast cancer (BC), and/or ovarian cancer (OC). Please tell us how frequently these comments were true for you during the past week, not at all, rarely, somewhat, or often.

During the past week:	Not at all	Rarely	Sometimes	Often
a. You thought about BC and/or OC when you didn't mean to.				
b. You had trouble falling asleep or staying asleep because of pictures or thoughts about BC and/or OC that came into your mind.				
c. You had waves of strong feelings about BC and/or OC.				
d. You had dreams about BC and/or OC.				
e. Pictures about BC and/or OC popped into your mind.				
f. Any reminder brought back feelings about BC and/or OC.				

21.Thinking about the choices that you are making please listen to the following comments some people make. Tell me whether you strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree for each statement that I read to you.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
a.These decisions are hard for me to make.	1	2	3	4	5
b. I'm not confident with my decisions.	1	2	3	4	5
c. It's clear which choices are best for me.	1	2	3	4	5
d. I'm aware of the management options I have to modify my risk.	1	2	3	4	5
e. I feel I know the benefits of the management options for my risk.	1	2	3	4	5
f. I am satisfied that I am adequately informed about the issues important to my decision.	1	2	3	4	5
g. I feel I know the risks and side effects of the management options for my risk.	1	2	3	4	5

h. I feel I am making an informed choice.	1	2	3	4	5
i. I am satisfied that these are my decisions to make.	1	2	3	4	5
j. I expect to successfully carry out the decisions that I am making.	1	2	3	4	5
k. I am satisfied that my decisions are consistent with my personal values.	1	2	3	4	5
l. The decisions that I am making are the best possible for me personally.	1	2	3	4	5

Appendix D

Decision Aid Instructions

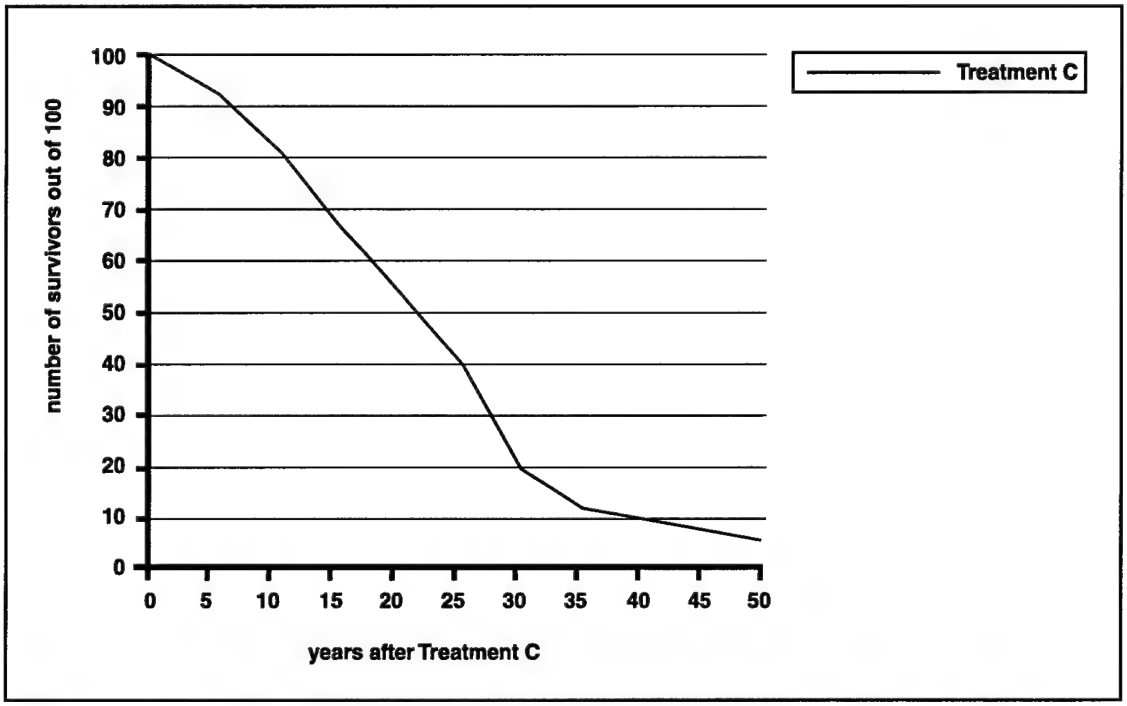
Sample Decision Aids

Decision Making for Women Managing their Cancer Risk

The information that you will find in this folder aims to help you make decisions about your cancer risk management. There are many options available to you to manage your risk of breast and ovarian cancer. Because every woman's situation varies according to personal and family health history, the information in this folder has been individualized for your particular situation. As you may remember, at the time you chose to participate in this study, we asked you some questions about your medical history, ranging from your age to whether you have had a heart attack. This information was entered into a computer model that computed your cancer risk according to several options that you have. In this folder, we use survival curves to show how different choices impact your personal risk. Each curve that you will be shown represents your management options, such as having a prophylactic mastectomy, and you will be able to layer these curves on top of each other in order to compare them and decide which is best for you.

To get the most out of this, we would like to make sure that you understand the curves that you are being shown. On the following pages you will find several curves with some brief questions about them. Please read the short introductions, answer the questions to the best of your knowledge, and review the answers on the back of the page. If you become uncomfortable while reviewing the folder, you are free to stop at any time. If you have any questions, please do not hesitate to ask your counselor.

Thank you for your participation in this study.



The graph above is a survival curve. It shows the number of people who are alive after having Treatment C for a condition. At year 0, 100 patients had surgery. The curve shows how many people are alive at different times after having Treatment C. For example, twenty years after Treatment C, 54 people are still alive. Please answer the following questions using the above graph.

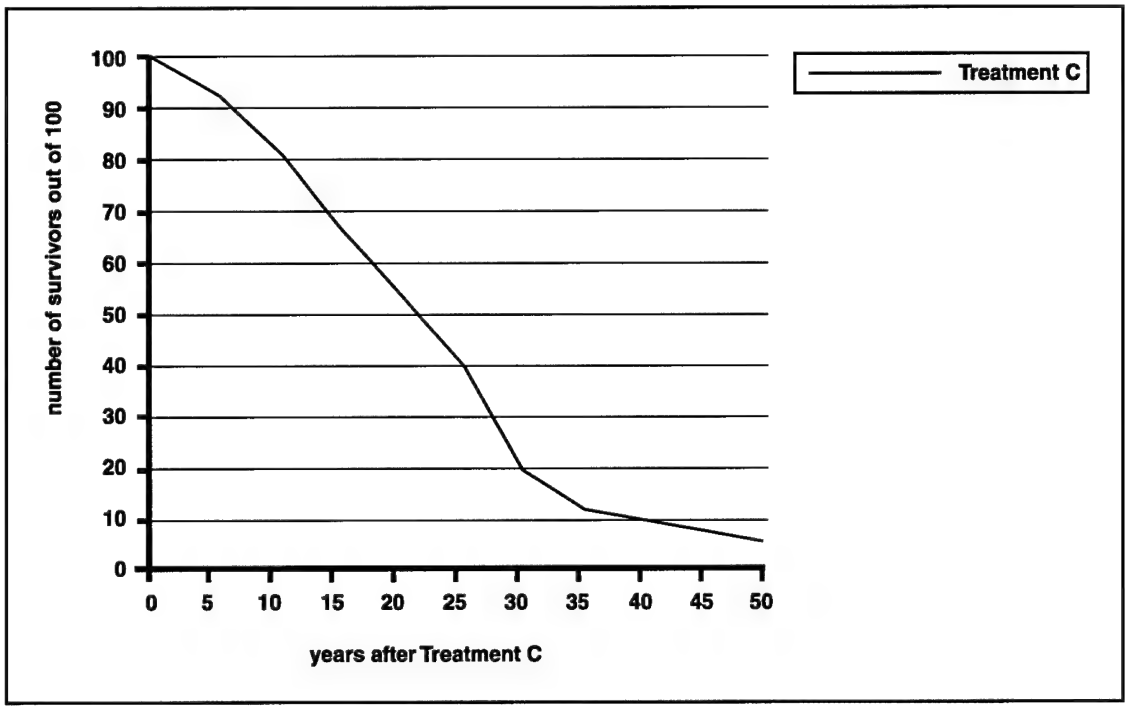
1. How many people are alive at year 0? _____

2. How many people are alive at year 25? _____

3. How many people died between year 0 and year 30? _____

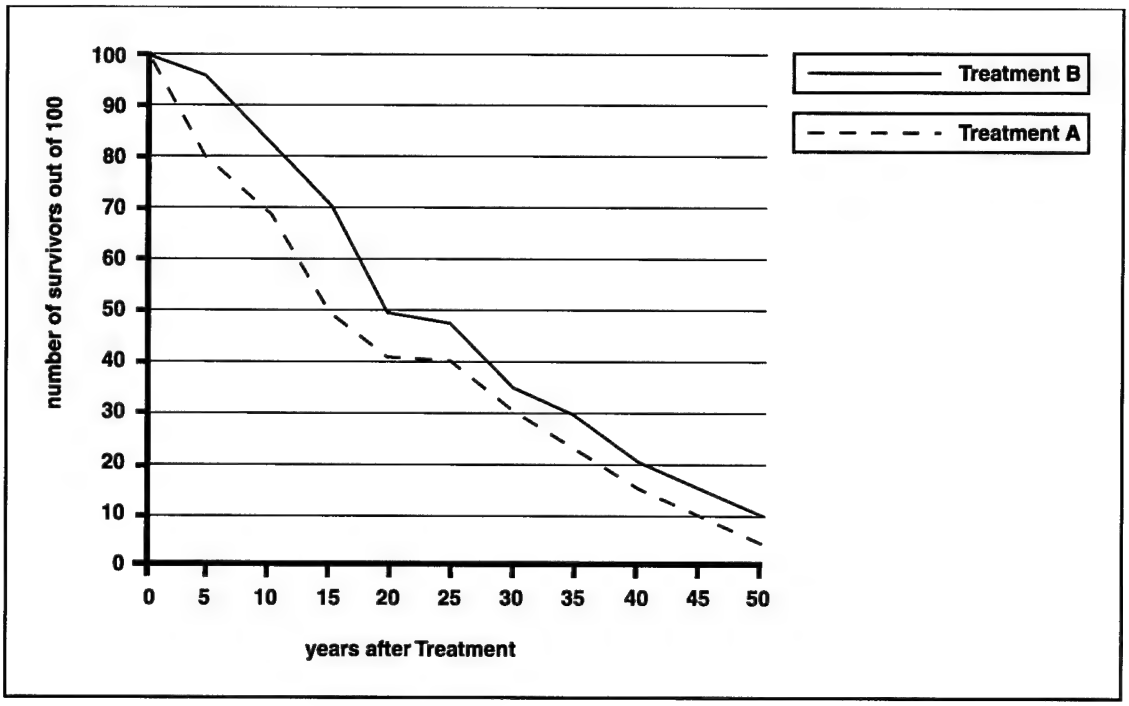
4. How many people are alive at year 35? _____

5. Did more people die between years 0 and 5 or between years 10 and 15? _____



Now, we will show you the correct responses to these questions about this graph. If you have trouble understanding any of these responses, please discuss them with your counselor. It is important that you understand this information so that you can get the most out of the information that we give you in this folder.

1. How many people are alive at year 0?	100
2. How many people are alive at year 25?	40
3. How many people died between year 0 and year 30?	80
4. How many people are alive at year 35?	About 12
5. Did more people die between years 0 and 5 or between years 10 and 15?	10-15



This graph has two survival curves that show how many people are alive after either having Treatment A or Treatment B for a condition. At year 0, 100 patients were given Treatment A and 100 patients were given Treatment B. The curve marked by the solid line shows the patients who had Treatment B. The curve marked by the dashed line shows the patients who had Treatment A. The curves show how many people are alive at different times after Treatment A or Treatment B.

1. How many people are alive at year 0 who receive Treatment A? _____

2. How many people are alive at year 0 who receive Treatment B? _____

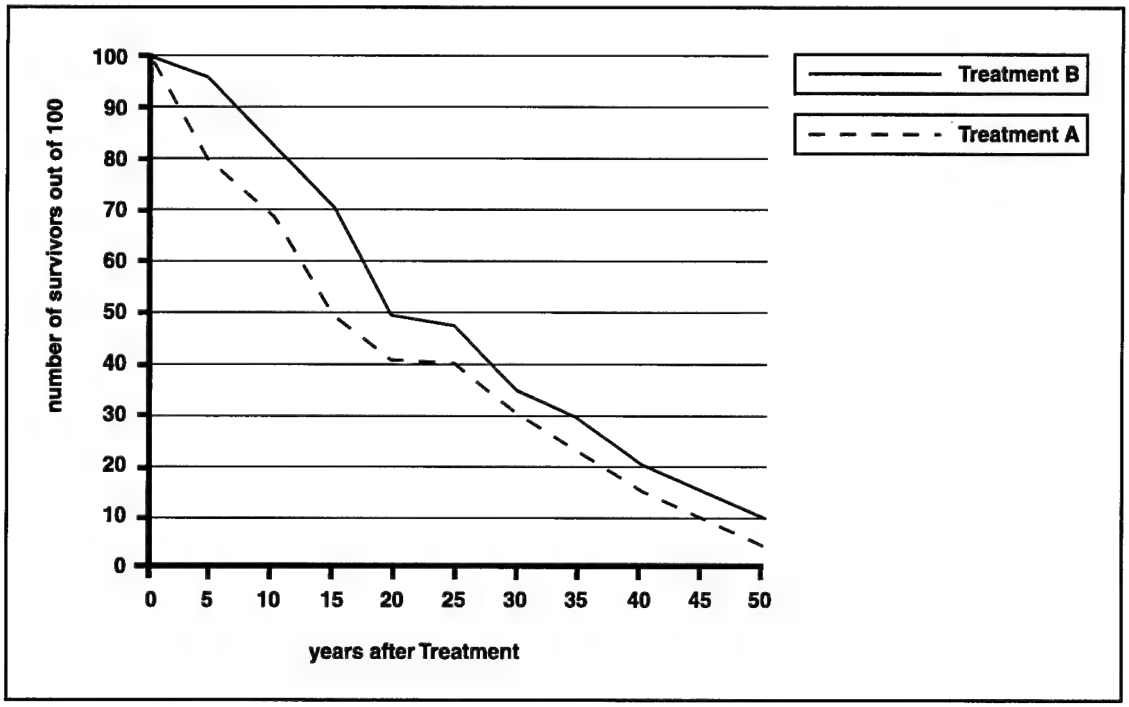
3. How many people are alive at year 15 who receive Treatment A? _____

4. How many people are alive at year 20 who receive Treatment B? _____

5. In which group are more people alive at year 30?

[ ] Treatment A
[ ] Treatment B

How many more are alive in this group at year 30? _____

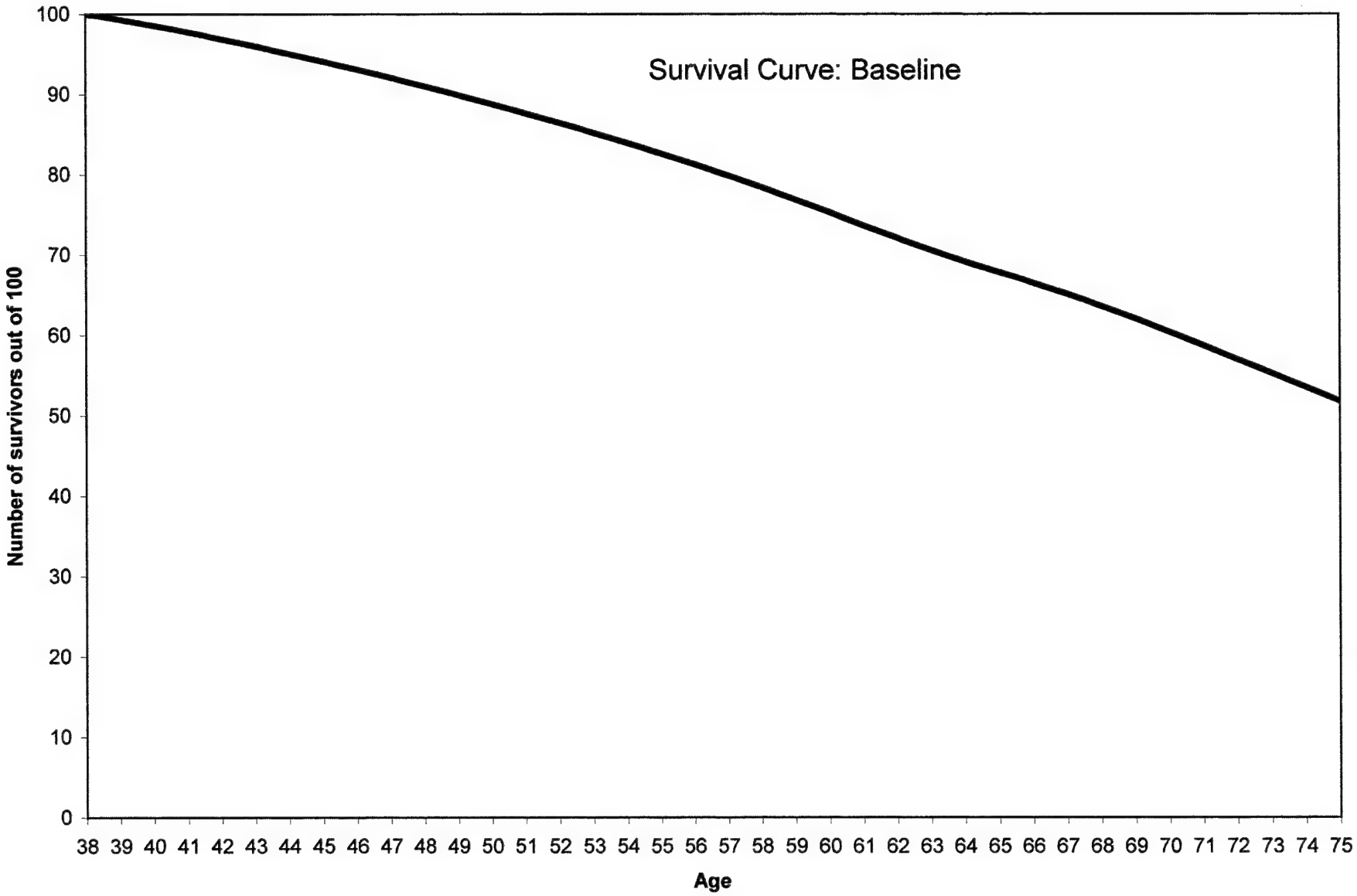


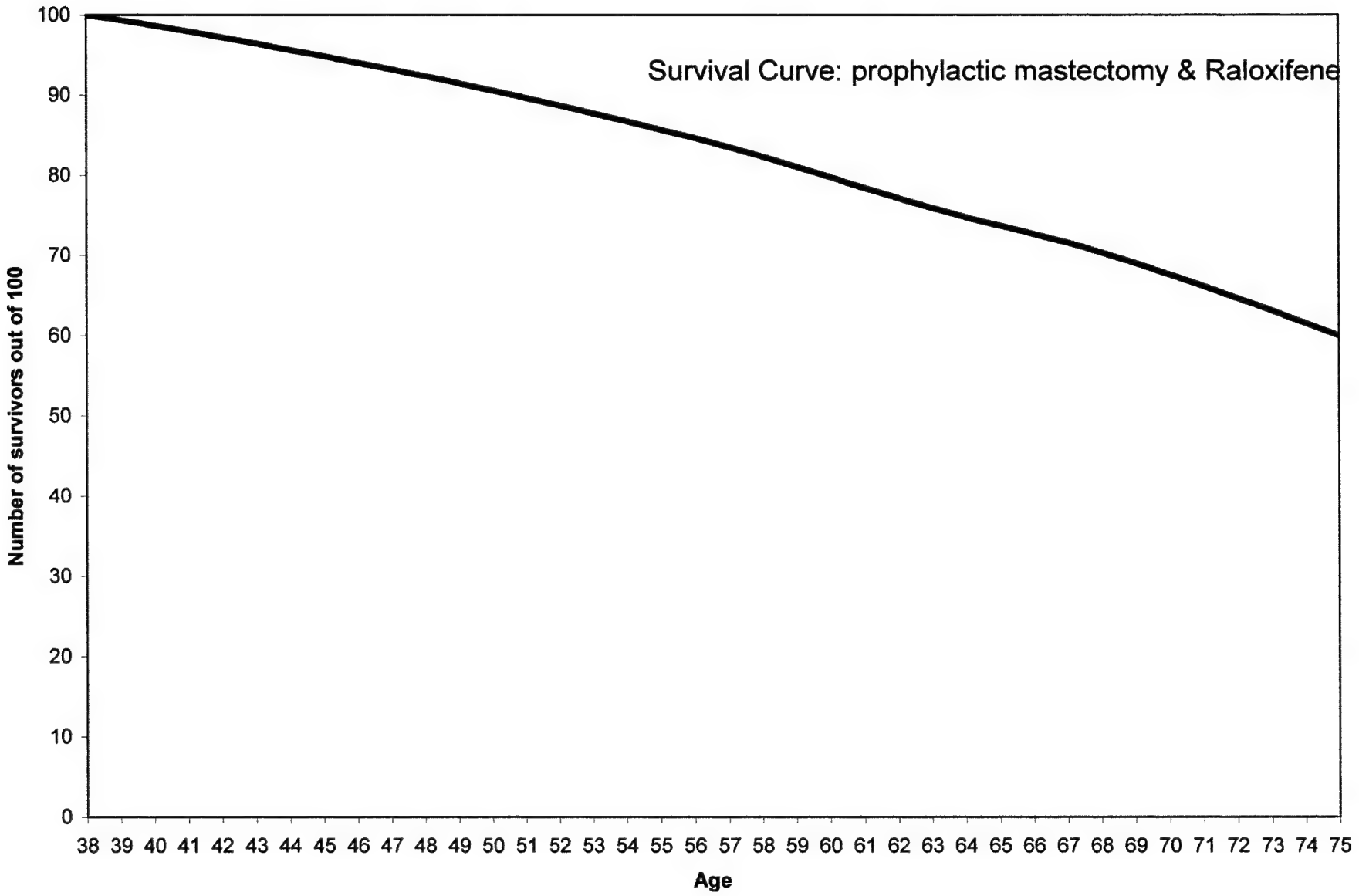
Now, we will show you the correct responses to these questions about this graph. If you have trouble understanding any of these responses, please discuss them with your counselor. It is important that you understand this information so that you can get the most out of the information that we give you in this folder.

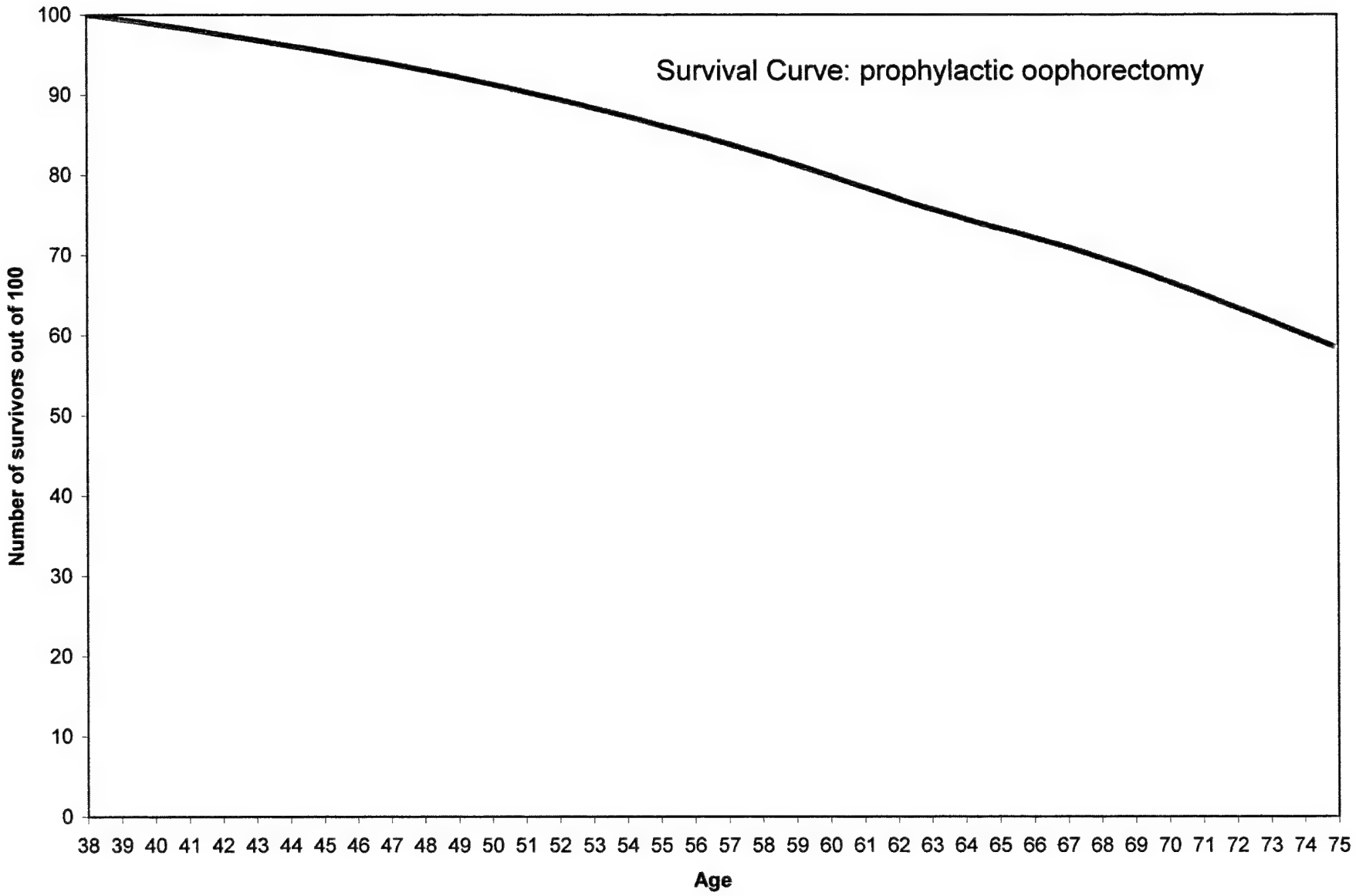
1. How many people are alive at year 0 who receive Treatment A?	100
2. How many people are alive at year 0 who receive Treatment B?	100
3. How many people are alive at year 15 who receive Treatment A?	50
4. How many people are alive at year 20 who receive Treatment B?	50
5. In which group are more people alive at year 30?	[ ] Treatment A [X] Treatment B
How many more are alive in this group at year 30?	5

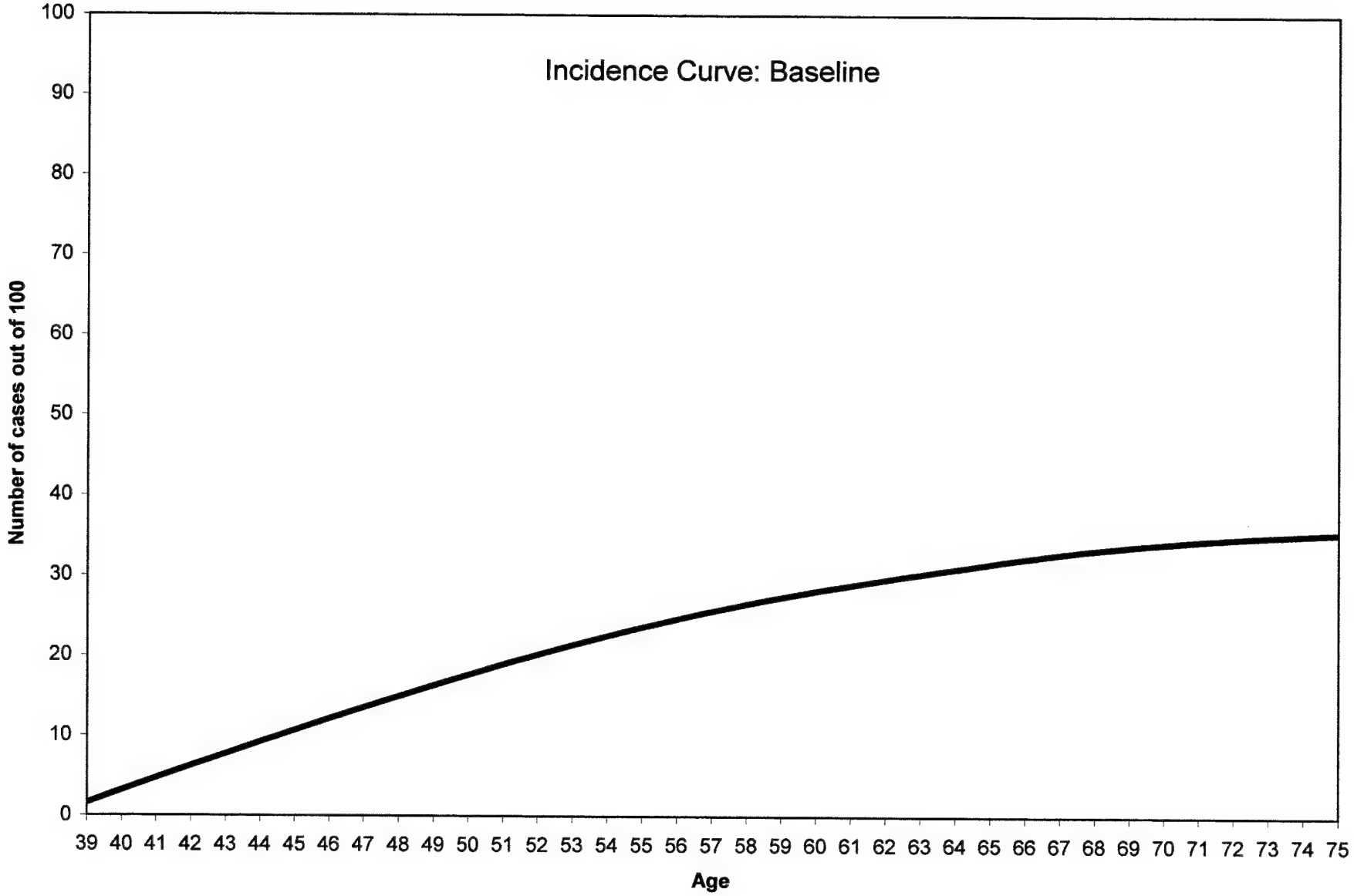
Baseline and intervention survival and Incidence curves of a BRCA positive patient with no history of:

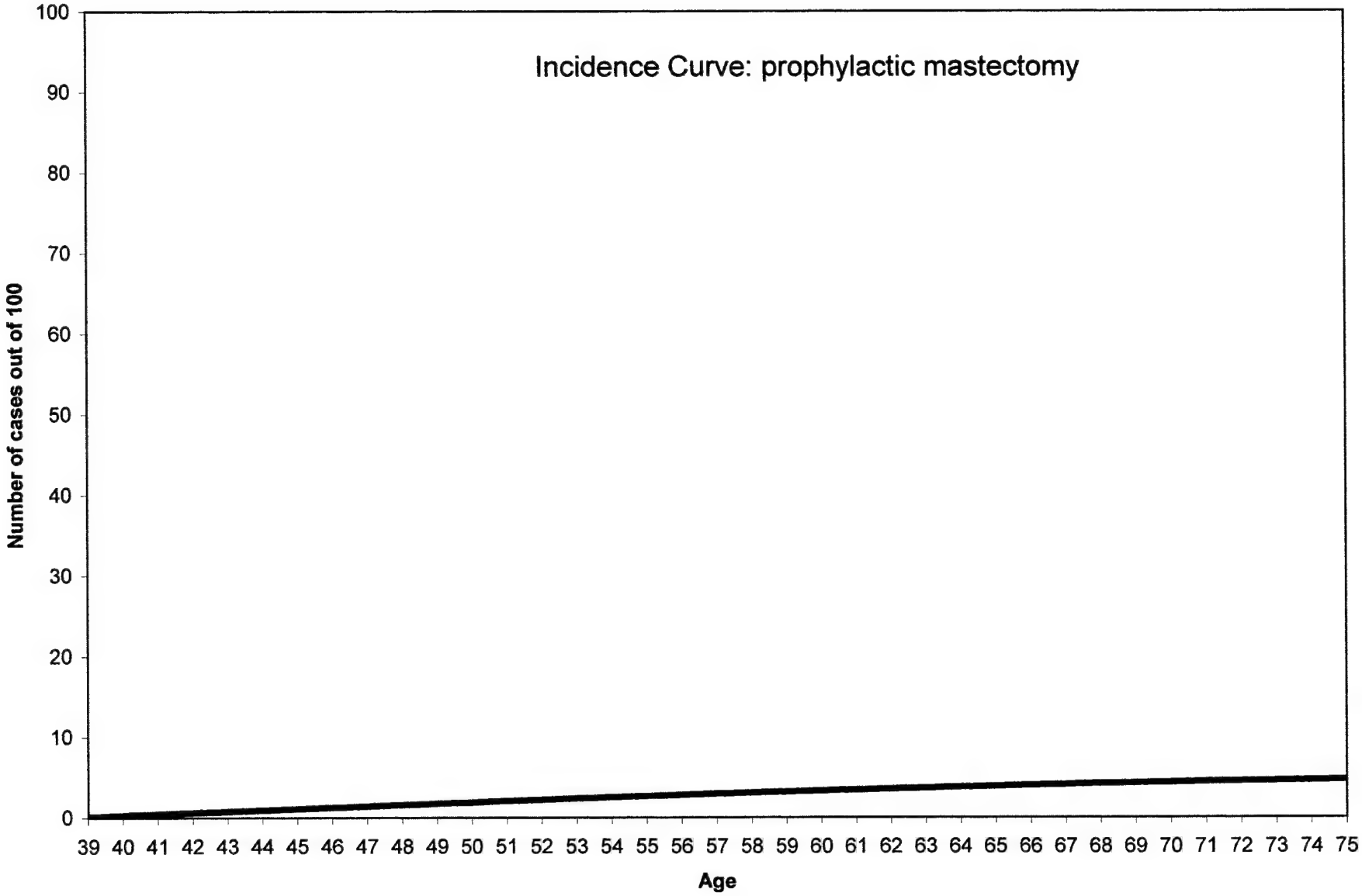
Diabetes
High blood pressure
High cholesterol
Cigarette smoking
Heart attack
Breast cancer

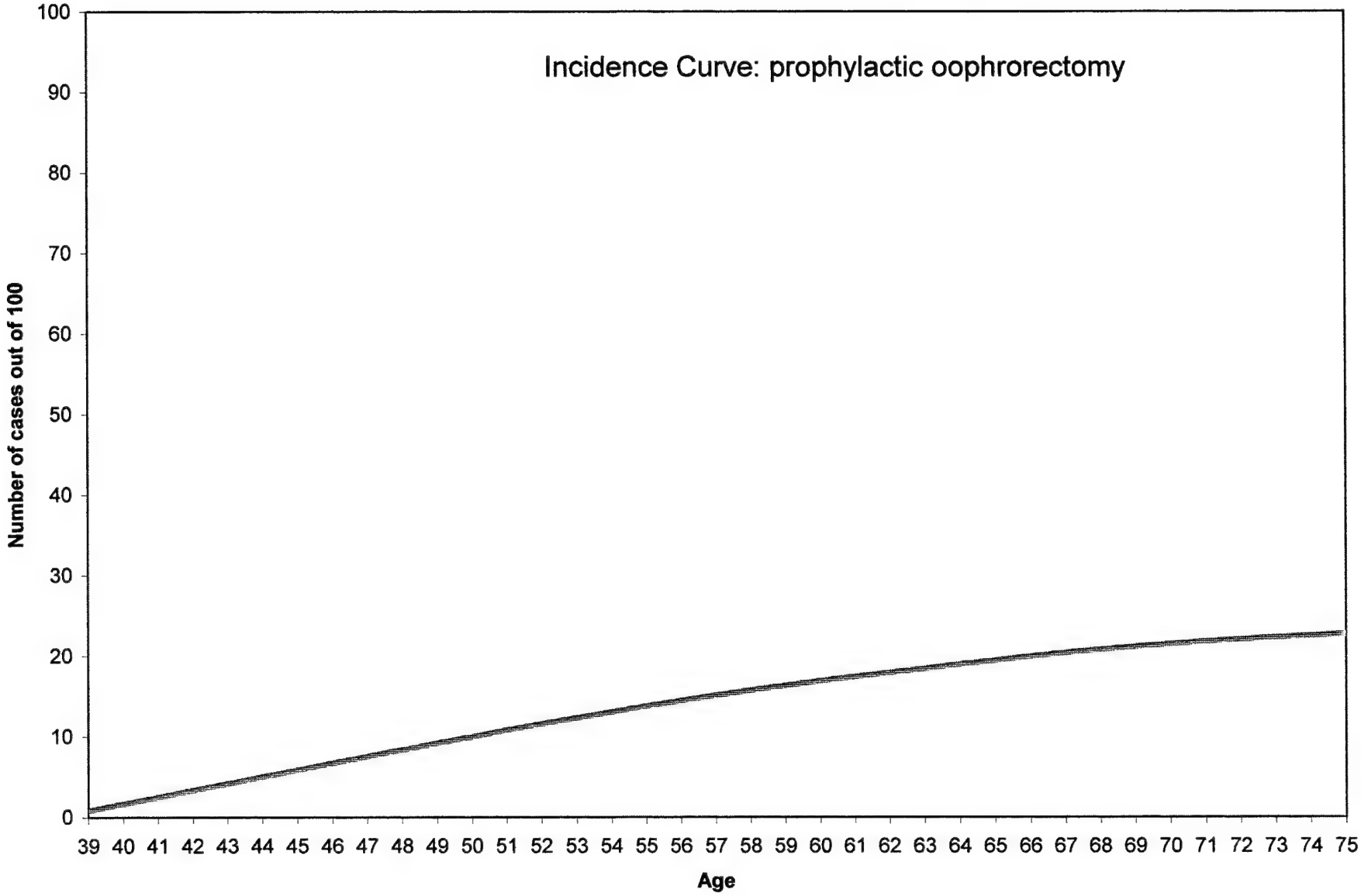

Survival Curve: Baseline
Number of survivors out of 100
100
90
80
70
60
50
40
30
20
10
0
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75
Age


Survival Curve: prophylactic mastectomy & Raloxifene
Number of survivors out of 100
100
90
80
70
60
50
40
30
20
10
0
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75
Age


Survival Curve: prophylactic oophorectomy
Number of survivors out of 100
100
90
80
70
60
50
40
30
20
10
0
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75
Age


Incidence Curve: Baseline
Number of cases out of 100
100
90
80
70
60
50
40
30
20
10
0
39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75
Age


Incidence Curve: prophylactic mastectomy
Number of cases out of 100
100
90
80
70
60
50
40
30
20
10
0
39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75
Age


Incidence Curve: prophylactic oophrorectomy
Number of cases out of 100
0
10
20
30
40
50
60
70
80
90
100
39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75
Age

Appendix E

Published Manuscripts

Short Communication

Factors Associated with Decisions about Clinical *BRCA1/2* Testing[1]

Katrina Armstrong,[2] Kathleen Calzone, Jill Stopfer, Genevieve Fitzgerald, James Coyne, and Barbara Weber

Department of Medicine [K. A., K. C., J. S., G. F., J. C., B. W.] and Center for Clinical Epidemiology and Biostatistics [K. A.], University of Pennsylvania School of Medicine, University of Pennsylvania Cancer Center [K. A., K. C., J. S., J. C., B. W.], and Leonard Davis Institute of Health Economics [K. A.], University of Pennsylvania, Philadelphia, Pennsylvania 19104

Abstract

Testing for mutations in *BRCA1* and *BRCA2* can provide important information about breast and ovarian cancer risk to a small but identifiable subgroup of women. Women who test positive for a *BRCA1/2* mutation can pursue more aggressive cancer surveillance and prevention regimens. Among families with known mutations, women who test negative may avoid unnecessary interventions. Currently, little is known about the factors associated with the use of clinical *BRCA1/2* testing. The objective of this study was to determine the factors associated with decisions about clinical *BRCA1/2* testing among women undergoing clinical *BRCA1/2* counseling through a retrospective cohort study of women who participated in a university-based clinic offering breast cancer risk assessment, genetic counseling, and *BRCA1/2* testing between January 1996 and April 1998. From the 251 eligible women who responded to a follow-up survey, 125 (50%) had undergone or were undergoing *BRCA1/2* testing, 86 (34%) had decided not to undergo testing, and 40 (16%) were undecided about testing. After multivariate adjustment, we found that women who chose to undergo *BRCA1/2* testing were more likely to have a known familial mutation [odds ratio (OR), 7.46; 95% confidence interval (CI), 0.97–62.16], more likely to be Ashkenazi Jewish (OR, 6.37; 95% CI, 2.68–15.12), more likely to want cancer risk information for family members (OR, 1.93; 95% CI, 0.99–4.14), more likely to want information about ovarian cancer risk (OR, 1.69; 95% CI, 1.18–3.69), and less likely to be concerned about insurance or job discrimination (OR, 0.45; 95% CI, 0.21–0.94). These associations were also found in the subgroup of women with a predicted probability of a *BRCA1* mutation of ≥5%. Our study suggests that approximately half of eligible women choose to undergo clinical *BRCA1/2* testing after participating in counseling. Women who have the highest risk of carrying a mutation, and thus the greatest probability of gaining some useful information from the test results, are most likely to undergo testing. Women who undergo testing are also more interested in ovarian cancer risk information and less concerned about job and insurance discrimination.

Introduction

Mutations in the cancer susceptibility genes *BRCA1* and *BRCA2* are associated with a significantly increased lifetime risk of breast and ovarian cancer (1, 2). Although interest in genetic testing for cancer susceptibility has grown quickly in the medical community, deciding about *BRCA1/2* testing remains a potentially complex and difficult process.

The primary benefit of *BRCA1/2* testing is the information that can be gained about individual and familial breast and ovarian cancer risk. This information may have significant implications for decisions about cancer surveillance and cancer prevention (3, 4). The limitations and risks of *BRCA1/2* testing are complex (4–6). Currently available options for cancer surveillance and prevention have limited efficacy and/or involve significant trade-offs (4). Furthermore, the cancer risk information gained from testing is limited in most contexts. Outside of families with known mutations, most women test negative and have little change in their predicted risk of breast or ovarian cancer (3). For these women, testing may be unlikely to affect their surveillance or risk reduction regimens. The adverse psychological consequences of positive or negative tests and employment, social, or insurance discrimination are often cited as potential drawbacks to undergoing *BRCA1/2* testing (5, 6). In addition, full *BRCA1/2* testing currently costs over $2,500, and insurance coverage is variable (7).

Currently, little information is available regarding the uptake of *BRCA1/2* testing in a clinical setting or the reason women decide against undergoing testing. To date, most studies have focused on high-risk families offered testing through research protocols (8, 9). The aims of our study were to determine the proportion of women who undergo *BRCA1/2* testing and the factors associated with decisions about *BRCA1/2* testing among women undergoing *BRCA1/2* counseling at a clinical breast cancer risk assessment program that offers genetic testing as a clinical service.

Materials and Methods

Study Setting. The University of Pennsylvania BCREP[3] is a multidisciplinary clinical program that provides breast cancer risk assessment, genetic counseling, and genetic testing for *BRCA1/2* mutations. The program has provided clinical testing for *BRCA1/2* mutations to women without cancer since October

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[1] K. A. is supported by American Cancer Society Clinical Research Training Grant CRTG9902301 and Department of the Army Breast Cancer Research Program Grant BC971623. B. W. is supported by the Breast Cancer Research Foundation and National Cancer Institute Grant CA57601.
[2] To whom requests for reprints should be addressed, at Department of Medicine, University of Pennsylvania School of Medicine, 1233 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021. Phone: (215) 898-0957; Fax: (215) 573-8778; E-mail: karmstro@mail.med.upenn.edu.

[3] The abbreviation used is: BCREP, Breast and Ovarian Cancer Risk Evaluation Program.

1996. Although research testing is offered selectively based on eligibility criteria, clinical testing is provided to any individual who chooses to undergo testing after participating in genetic counseling. Women with an estimated probability of a *BRCA1/2* mutation of <5% are counseled that they are unlikely to gain information from testing. During this study, estimates of the probability of *BRCA1* mutation were provided using a prediction model developed by Couch *et al* (10). A similar *BRCA2* prediction model did not exist at the time of the study. On the basis of the population genetics of *BRCA1/2*, non-Ashkenazi women were told their risk of *BRCA2* mutation was about half that of *BRCA1*, whereas Ashkenazi women were told their risk of *BRCA2* mutation was equivalent to that of *BRCA1* (11). Women who were not considering undergoing *BRCA1/2* testing at the time of their visit to BCREP received individualized information about breast and ovarian cancer risk and surveillance recommendations but did not undergo full pretest genetic counseling.

Study Design and Subject Selection. A total of 518 individuals participated in the BCREP between January 1995 and April 1998. Women who had previously requested not to participate in further research ($n = 22$) and men ($n = 6$) were excluded. In October 1998, all of the eligible subjects ($n = 490$) were mailed a questionnaire, a letter, and a stamped, addressed envelope. Subjects who did not respond were mailed two reminder letters, including questionnaires. The study protocol was approved by the Institutional Review Board of the University of Pennsylvania.

Data Collection. To identify factors that were associated with decisions about genetic testing, four focus groups of women ($n = 16$) who had participated in the BCREP were held. In each group, women were asked to list all of the issues that had influenced their decision about genetic testing. A questionnaire was developed that asked respondents to rate the importance of each factor identified in the focus groups on a four-point Likert response scale (very important, moderately important, a little important, and not at all important). These factors are listed in Table 2. In addition, the questionnaire asked subjects if they had already undergone testing, had decided to undergo testing in the future, were undecided about testing, or had decided not to undergo testing. Sociodemographic characteristics and family history of breast cancer were obtained from clinical records.

Statistical Analysis. Predicted lifetime risks of breast cancer for subjects without a diagnosis of breast cancer were calculated from prediction tables developed by Claus *et al* (12). Predicted risks of *BRCA1* mutation for the BCREP population were calculated from tables developed by Couch *et al.*(10). Because these risks had skewed distributions, Wilcoxon's rank-sum test was used in confirmatory analyses. For the primary analysis, women were characterized by self-report as having decided not to undergo testing (declined testing group) or undergoing/having undergone testing (tested group). Women who were undecided about testing were excluded. Associations between each variable and the testing decision were examined using Wilcoxon's rank-sum test for ordered variables (*i.e.,* importance rated on a four-point scale) and the ordinary χ^2 test for dichotomous variables (*e.g.,* very important *versus* other). Multivariable analyses were conducted using multiple logistic regression. Because of correlations between concerns about health insurance, life insurance, and job discrimination and between the importance of ovarian cancer risk information and the importance of help deciding about prophylactic oophorectomy, composite variables were constructed to represent concern about discrimination from testing and interest in information about ovarian cancer risk. No other significant correlations were identified between variables associated with testing in this sample, including Ashkenazi background and presence of familial mutation. Each variable associated with testing in bivariate analysis at $P \leq 0.10$ was tested for inclusion in the model. The final model included all of the variables whose inclusion altered the odds ratio for another variable by ≥10%. Because of concern that women might perceive the factors that influenced their decisions differently over time and according to their test results, we tested interaction terms for calendar time since counseling and *BRCA1/2* test results. To understand the factors that affected testing decisions among women who had an elevated risk of carrying a mutation, we repeated our analyses in the subgroup of women with a predicted probability of *BRCA1* mutation of ≥5%.

Table 1 Subject characteristics

	Overall ($n = 211$)	Testing ($n = 125$)	Declined testing ($n = 86$)	Two-tailed *P*
Mean age, yrs (range)	44.6 (24–73)	45.8 (24–73)	42.7 (27–73)	0.04
Caucasian (%)	96.8	98.1	94.6	0.21
Ashkenazi (%)	29.9	42.9	13.3	0.0005
College education (%)	73.6	77.6	71.7	0.49
Employed (%)	74.0	74.1	77.3	0.72
Breast cancer (%)	30.9	36.5	22.7	0.04
Known familial mutation	6.2	9.7	1.1	0.04
Predicted breast cancer risk, mean (SD)[a]	0.24 (0.13)	0.26	0.21	0.03
Predicted *BRCA1* risk, mean (SD)	0.18 (0.20)	0.24 (0.23)	0.10 (0.07)	<0.0005

[a] Among women without a breast cancer diagnosis.

Results

Of the 490 women to whom surveys were mailed, 10 women had died, and 36 women had moved. A total of 353 women returned completed surveys for a response rate of 80%. Nonresponders did not differ from responders in age, predicted risk of breast cancer, or predicted risk of a *BRCA1* mutation in the family (*Ps* > 0.1). Eighteen women who were not considering undergoing *BRCA1/2* testing at the time of their visit, 76 women who were seen before *BRCA1/2* testing was offered to women without cancer outside of a research protocol, and 8 women who pursued testing through a research protocol were excluded from these analyses. Of the remaining 251 eligible women, 125 (50%) women had undergone *BRCA1/2* testing or were undergoing testing, 86 (34%) had decided not to undergo testing, and 40 (16%) were undecided about testing (including 14 women who had a family member pursuing testing).

The characteristics of women who underwent testing and women who decided not to undergo testing are reported in Table 1. Women who underwent testing were older and more likely to be Ashkenazi Jewish, to have a diagnosis of breast cancer, and to have a known familial *BRCA1* or *BRCA2* mutation than women who declined testing. Women who underwent testing had a slightly higher risk of breast cancer and a substantially higher risk of carrying a *BRCA1* mutation than women who declined testing.

Women who underwent testing were significantly more likely to rank several potential benefits of testing as very important in their decision (Table 2). These benefits included providing cancer risk information for family members, learning information about ovarian cancer risk, and obtaining help in

Table 2 Benefits, risks, and limitations of *BRCA1/2* testing (reported as the percentage of subjects rating a factor very important)

Factors	Testing (n = 125)	Declined testing (n = 86)	Two-tailed P
Learning about my breast cancer risk	76.3	73.8	0.69
Learning about my ovarian cancer risk	76.1	57.5	0.005
Providing information for family members	75.8	56.3	0.003
Help deciding about prophylactic mastectomy	38.7	21.5	0.01
Help deciding about prophylactic oophorectomy	59.1	29.5	0.0001
Help deciding about estrogen replacement	29.9	28.8	0.89
Desire to be reassured if test was negative	73.9	69.7	0.52
Concern about my anxiety if test was positive	36.7	46.3	0.17
Fear of health insurance discrimination	36.1	47.1	0.11
Fear of life insurance discrimination	28.1	42.2	0.04
Fear of job discrimination	12.4	27.7	0.006
Cost of the test	22.3	22.9	0.74
My doctor's recommendation	39.3	32.1	0.30
My family's recommendation	30.7	30.0	0.96
Desire to help advance research	46.3	40.0	0.37

Table 3 Adjusted associations with undergoing testing (n = 169)

	OR[a]	95% CI[b]	Two-tailed P
Familial mutation	7.46	0.97–62.16	0.06
Ashkenazi background	6.37	2.68–15.12	0.0005
Importance of			
Information for family members	1.93	0.99–4.14	0.05
Information about ovarian cancer risk	1.69	1.18–3.69	0.009
Fear of insurance discrimination	0.45	0.21–0.94	0.03

[a] OR, odds ratio.
[b] CI, confidence interval.

deciding about prophylactic oophorectomy and prophylactic mastectomy. Conversely, concerns about life insurance and job discrimination were more likely to be considered very important by women who declined testing. After multivariable analyses, Ashkenazi background, known familial mutation, fear of insurance discrimination, importance of information for family members, and importance of information about ovarian cancer risk remained associated with use of testing (Table 3). No interaction was found between the effects of these factors and calendar time since counseling or *BRCA1/2* test results (Ps > 0.2).

Among the subgroup of women (n = 206) with a predicted probability of a *BRCA1* mutation of ≥5%, 60 (29%) women had declined testing, 116 (56%) women had chosen to undergo testing, and 30 (15%) women were undecided (including 11 women who had a family member pursuing testing). After multivariable adjustment, there were no substantial differences between the associations with testing decisions in this subgroup and those associations found in the entire sample (data not shown).

Discussion

This study suggests that approximately two-thirds of women considering *BRCA1/2* testing at the time of their visit to a clinical cancer risk evaluation program decide to undergo testing after participating in counseling. Women who undergo testing are at higher risk of carrying a *BRCA1* mutation, more likely to want information about ovarian cancer risk for themselves and about breast and ovarian cancer risk for family members, more likely to be Ashkenazi Jewish, more likely to have a known familial mutation, and less likely to be concerned about insurance or job discrimination. The association with risk of *BRCA1* mutation is present whether measured by predicted probabilities, the presence of familial mutation, or the presence of risk factors, *i.e.,* Ashkenazi Jewish heritage.

The associations between the risk of carrying a mutation, a known familial mutation, and gaining risk information for family members and decisions about *BRCA1/2* testing are reassuring. Most experts agree that *BRCA1/2* testing should be targeted to women who are most likely to gain useful information from testing (13, 14). Women at higher risk of carrying a mutation are more likely to be found to carry a mutation, more likely to gain useful information, and should be more likely to decide to get tested. Women with a familial mutation will also gain more information from a negative test, because the cause of their familial predisposition has been identified. Furthermore, because of the potential implications of genetic testing for family members, more information is gained from *BRCA1/2* testing when the results are salient to other family members.

The relatively greater importance of ovarian cancer risk information is likely to be multifactorial. First, prophylactic oophorectomy may appeal to more women than prophylactic mastectomy, both because prophylactic mastectomy is a more extensive and potentially disfiguring procedure and because substantially more evidence exists supporting the efficacy of breast cancer surveillance than that of ovarian cancer surveillance (15–17). Second, for the majority of women concerned about their increased breast cancer risk at the time they seek *BRCA1/2* counseling, finding a *BRCA1/2* mutation only confirms their belief in their increased risk. The information that testing may bring about ovarian cancer risk may seem like the bigger change. Third, *BRCA1/2* testing was the only method available to assess individual ovarian cancer risk at the time of this study, whereas several models were available to predict breast cancer risk (18).

Although there is little evidence suggesting that insurance discrimination is occurring at present, the association between fear of insurance or job discrimination and decisions about *BRCA1/2* testing is disconcerting. Because genetic information cannot be taken back once received, many women are reluctant to pursue testing without assurance that discrimination could not occur in the future. This situation is particularly paradoxical if women who would have been found to carry a mutation and taken steps to lower their cancer risk decline testing because of fear of insurance discrimination. Information gained from *BRCA1/2* testing that results in women choosing interventions that lower their risk of cancer is good for everyone concerned, including life and health insurers.

This study both extends and supports the findings of prior studies of decisions about *BRCA1/2* testing. Prior studies using hypothetical scenarios generally found a majority of women reported interest in testing, and interest in testing was higher among women with a higher perceived risk of carrying a mutation, greater concerns about cancer risk, and more interest in getting information for family members (19–23). Conversely, studies of research family members found that <50% of participants requested their genetic test results; however, participants requesting results also rated the benefits of testing

more highly, knew more about *BRCA1* testing, and had more first-degree relatives with breast cancer (8, 9).

Because this study was conducted retrospectively, the decision about testing may have influenced the perceptions and reporting of the factors that were important in that decision. We cannot determine to what degree women may have adopted beliefs after they made their decision to support or justify their behavior (24). In addition, the factors that women felt were most important in their decision about *BRCA1/2* testing may have changed over time. Establishing a single time when decisions are made about testing is difficult. In our sample, almost a fifth of women were still undecided about testing up to 2 years after counseling. The time point for this study was selected to minimize the number of women who were undecided about testing while maintaining reasonable proximity to the date of counseling. Although the cost of testing was not an important factor in our study, our sample was highly educated and thus likely to be relatively affluent. Cost may be an important barrier to testing in less affluent populations. Finally, the generalizability of these results to women currently participating in similar programs is unknown.

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Effect of Framing as Gain versus Loss on Understanding and Hypothetical Treatment Choices: Survival and Mortality Curves

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Background. *Presentation of information using survival or mortality (i.e., incidence) curves offers a potentially powerful method of communication because such curves provide information about risk over time in a relatively simple graphic format. However, the effect of framing as survival versus mortality on understanding and treatment choice is not known.* ***Methods***. *In this study, 451 individuals awaiting jury duty at the Philadelphia City Courthouse were randomized to receive 1 of 3 questionnaires: (1) survival curves, (2) mortality curves, or (3) both survival and mortality curves. Each questionnaire included a brief description of a hypothetical treatment decision, survival curve graphs and/or mortality curve graphs presenting the outcome of the treatment, and questions measuring understanding of the information contained in the graphs and preference for undergoing treatment. After completing a brief practice exercise, participants were asked to answer questions assessing their ability to interpret single points on a curve and the difference between curves, and then to decide whether they would choose to undergo preventive surgery for 3 different scenarios in which the benefit of surgery varied.* ***Results***. *Participants who received only survival curves or who received both survival and mortality curves were significantly more accurate in answering questions about the information than participants who received only mortality curves ($P < 0.05$). For 2 of the 3 treatment presentations, participants who received only mortality curves were significantly less likely to prefer preventive surgery than participants who received survival curves only or both survival and mortality curves ($P < 0.05$). The effect of framing on understanding was greatest among participants with less than a college education and among non-Caucasian participants.* ***Conclusion***. *Framing graphic risk information as chance of death over time results in lower levels of understanding and less interest in preventive surgery than framing as chance of survival over time.* ***Key words:*** *Decision making; framing effect; risk communication.* ***(Med Decis Making 2002;22:76–83)***

Survival curves are a potentially powerful tool to communicate information about the outcomes of alternative choices.[1] Because survival curves provide a graphic presentation of the risk of an outcome over time, they include a large amount of information that is difficult to convey with numbers alone.[2,3] Furthermore, use of survival curves avoids the problem of having to select which time points to present—a selection that has been shown to influence choice.[4]

Presentation of probabilistic information as gain versus loss has been demonstrated to influence decision making.[5–10] Patients presented with surgical mortality as a 10% chance of dying are less likely to choose surgery than patients presented with surgical mortality as a 90% chance of surviving.[5] Because of the power of this framing effect, many experts argue that information should be presented in both formats in an attempt to "unbias" the presentation.[10,11]

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Presentation of graphic information about the probability of dying over time can also be framed as a gain or a loss using survival or mortality curves. Although several other framing effects have been demonstrated with survival curves, the effect of framing information as survival curves versus mortality curves is not known.[4,12–14] Furthermore, although presentation of both gain and loss formats may reduce the bias from presenting 1 format only, it greatly increases the complexity of the presentation and may decrease understanding. Thus, the aims of our study were to determine whether framing of information as survival curves or mortality curves affects understanding of the information or the preferred alternative, and whether presenting both survival and mortality curves reduces framing effects.

Methods

DESIGN

We conducted an experiment that compared the effects of presenting the same information about the outcomes of a hypothetical medical decision as (1) probability of surviving over time (survival curves), (2) probability of dying over time (mortality curves), or (3) probability of surviving and probability of dying (survival and mortality curves). Outcomes included understanding of the information and treatment preference and were measured using questions that were consistent with the format of the curves (i.e., questions about mortality curves asked the number of people who had died and questions about survival curves asked the number of people still alive). The study protocol was approved by the Human Subjects Committee of the Institutional Review Board at the University of Pennsylvania.

SETTING AND PARTICIPANTS

Prospective jurors awaiting jury selection at the Philadelphia City Courthouse were offered a candy bar to complete a study questionnaire. When all prospective jurors were assembled in a single room, a research assistant made an announcement about the survey and randomly distributed questionnaires to volunteers. Based on our experience with this method, we estimate that approximately 75% of prospective jurors volunteer to participate and more than 90% of individuals who volunteer complete the questionnaires. In Philadelphia, individuals are randomly selected for jury duty from voter registration and drivers license records.

INTERVENTION

Three versions of a questionnaire were developed: survival curves only, mortality curves only, and survival and mortality curves. For each version, care was taken to ensure that the presentation of information throughout the questionnaire was consistent with the framing selected. Versions were randomly distributed to study participants.

Each questionnaire began with a brief explanation of survival and/or mortality curves and a graph showing a single curve with 4 questions asking the number of people alive at different points in time. The explanation of survival curves read as follows:

> A survival curve is a picture that shows how long people live after being diagnosed with or treated for a disease. Survival curves are shown to patients to help them understand their disease and to decide which treatment option is best for them.

After the graph containing a single survival curve, the explanation continued:

> The above graph is a survival curve. It shows the number of people who survive after being diagnosed with an imaginary condition, Chocolitis. It begins in the upper left-hand corner with 100 patients diagnosed at year 0. The graph shows how many people are alive every 5 years after being diagnosed.

The explanation of mortality curves read as follows:

> A mortality curve shows the number of people who die after being diagnosed with or treated for a disease. These graphs are shown to patients to help them understand their disease and to decide which treatment option is best for them.

After the graph containing a single mortality curve, the explanation continued:

> The above graph is a mortality curve. It shows the number of people who die after being diagnosed with an imaginary condition, Soapoperitis. It begins in the lower left-hand corner with 100 patients diagnosed at year 0. The graph shows how many people died every 5 years after being diagnosed.

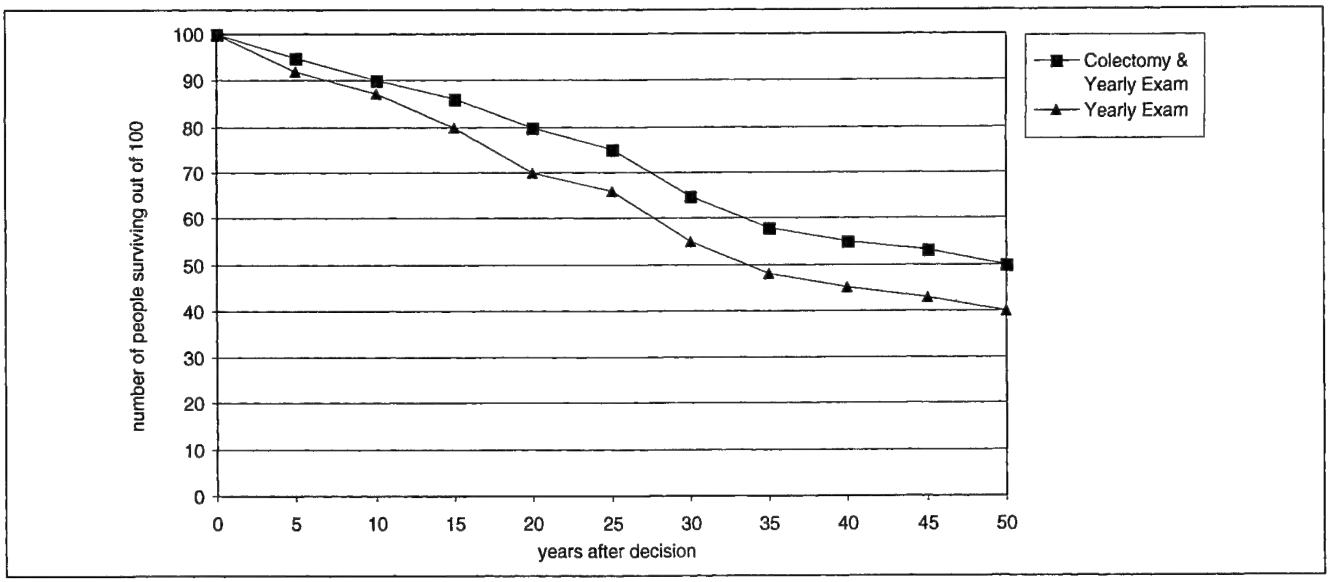

Figure 1. Survival curve graph.

We found this single-curve introduction improved understanding of graphs with 2 survival curves in a previous study. The questionnaire then presented a hypothetical scenario requiring a decision about a preventive treatment, graph(s) containing curves illustrating the chance of survival/death after the 2 possible choices, and outcome measurement questions. The hypothetical scenario read as follows:

> Imagine you are at increased risk of developing colon cancer. Yearly exams with a physician are recommended for everyone at increased risk for colon cancer. In addition to a yearly exam, you can choose to have a colectomy (removal of part of your colon) along with a colostomy (a plastic bag attached to your abdomen into which you empty your bowels). This procedure results in a lowered risk of developing colon cancer. The graph(s) on the facing page shows what we would expect to happen to 100 people just like you if they chose to have a colectomy with a colostomy or to have no surgery.

For each version of the questionnaire, the same size graph or graphs were presented on the left-hand page of a booklet with questions about the graph(s) on the right-hand page. For the questionnaire presenting both survival and mortality curves, survival curves were shown on the top graph and mortality curves on the bottom graph with an explanation that both graphs showed the same information about what was expected to happen. Figure 1 shows the survival curve graph, and Figure 2 shows the mortality curve graph.

OUTCOME MEASURES

We measured understanding by asking participants to interpret the number of people alive (or dead) at a point in time on a given curve (e.g., "How many people who have a colectomy are alive at year 20?"), determine which choice results in more people alive (or dead) at a point in time (e.g., "In which group are more people alive at year 30?"), and calculate the difference in the number of people alive (or dead) between curves at a point in time (e.g., "How many more people are alive in this group at year 10?"). The framing of the questions (alive vs. dead) mirrored the framing of the curves. For the questionnaire presenting both survival and mortality curves, an explanation was provided about the relationship between the number of people alive (based on the survival curve) and the number of people dead (based on the mortality curve) at any point in time. We measured treatment and preference by asking participants to decide whether they would want to have a preventive colectomy (i.e., "Given this information, which option would you choose?"). To determine whether framing as survival versus mortality affected the transitivity of preferences, we asked about preference for surgery at 3 levels of benefit of colectomy, each shown by a separate graph with 2 curves. We refer to these 3 levels of benefit by the proportional increase in absolute survival (5%, 10%, or 20% at 50 years) in this article. These relative percentages were not included on the graphs. For all questionnaires, the 10% gain in survival was presented first, followed by the 5% gain and then the 20% gain.

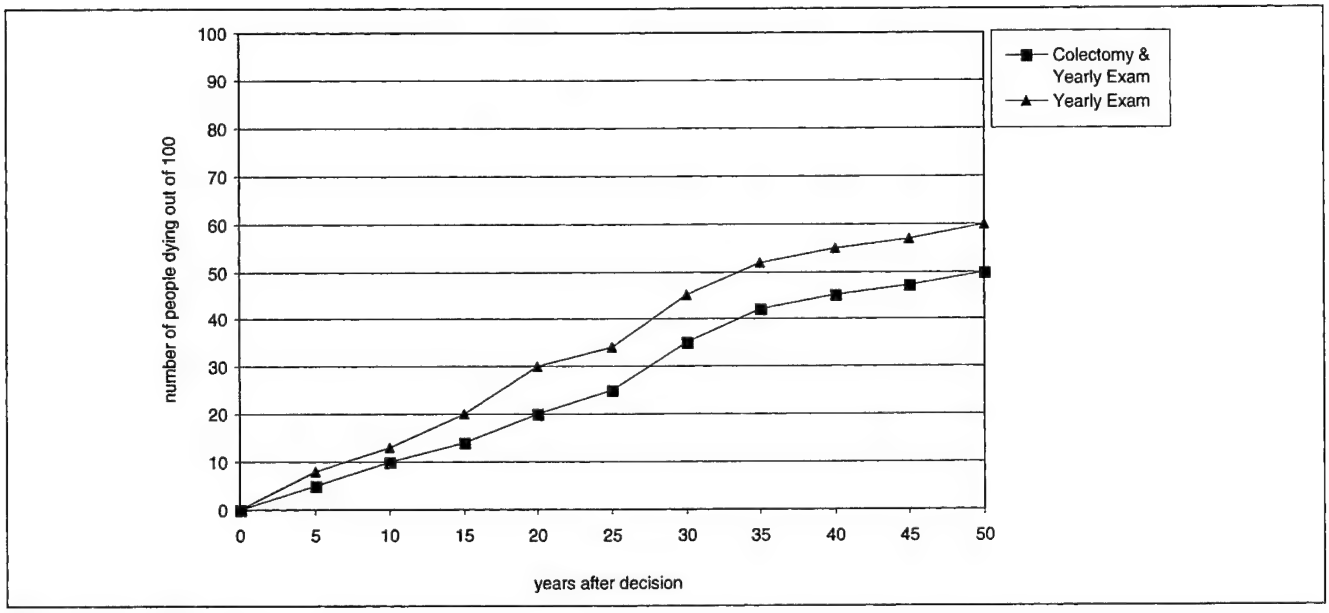

Figure 2. Mortality curve graph.

STATISTICAL ANALYSIS

Baseline characteristics of the 3 groups were compared using chi-square tests for categorical variables and analysis of variance followed by pairwise *t* tests for continuous variables. Three types of accuracy were measured: (1) interpretation of number of people alive or dead in a single group at a point in time, (2) determination of which group had more alive or dead at a point in time, and (3) calculation of the difference in number of people alive or dead between groups at a point in time. Two questions were included for each type. Participants were categorized as accurate if they answered both questions correctly, partially accurate if they answered 1 of the 2 questions correctly, and inaccurate if they answered neither question correctly. For the purposes of these analyses, these categories were dichotomized into accurate and not accurate (which included both partially accurate and inaccurate). Chi-square tests were used to compare the proportion of people who answered accurately and the proportion of participants who preferred surgery at each level of benefit between groups.

Multivariate analyses were conducted to assess the impact of gender, race, education, and age on the effect of framing on understanding and choice and the impact of understanding on choice. For these analyses, a single composite understanding variable was created that was coded 1 if participants answered all of the understanding questions correctly and 0 if they had any incorrect answers. Separate logistic regression models were constructed with understanding as the dependent variable and with preference as the dependent variable. The independent variables in the understanding model were frame, age, gender, education (high school vs. more than high school), and race (Caucasian vs. non-Caucasian). The independent variables in the preference model were frame, understanding, age, gender, education (high school vs. more than high school), and race (Caucasian vs. non-Caucasian). Variables were kept in the model if they were significantly associated with the dependent variable according to a Wald test ($P < 0.05$) or altered the coefficient for another variable by more than 15%. In addition, for each model, interaction terms were tested for potential interactions between the information frame (survival, mortality, or both) and demographic characteristics. Likelihood ratio tests were used to determine whether the interaction terms were significant. For interaction terms that were significant according to the likelihood ratio tests, Wald tests were used to identify the specific source of the interaction. Subsequent secondary analyses were conducted with level of understanding as a continuous variable (i.e., proportion of understanding questions answered correctly). However, because the conclusions of these analyses were the same as when understanding was analyzed as a categorical variable, we present only the categorical analyses. All *P* values are 2-sided.

Table 1 Subject Characteristics

	Mortality Curve	Both Curves	Survival Curve
Mean age (range)	42.9 (18-79)	42.6 (20-76)	41.2 (20-72)
Female	70%	65%	72%
Caucasian	52%	55%	46%
African American	40%	38%	45%
Mean years of education (range)	13.7 (8-17)	14.1 (9-19)	13.4 (8-17)

Results

We recruited a total of 451 participants, of whom 150 received the survival curve format, 151 received the mortality curve format, and 150 received the survival and mortality curve format. The 3 groups were not statistically different in age, gender, education, and ethnicity ($P > 0.6$) (Table 1).

EFFECT OF FRAMING ON UNDERSTANDING

Participants who received the information framed as survival curves or survival and mortality curves were more likely to accurately answer questions about the information than participants who received the information framed as mortality curves. This effect was seen for the ability (1) to interpret the number of people alive (or dead) in each treatment group at a point in time, (2) to determine which choice resulted in more people alive at a point in time, and (3) to calculate the difference in the number of people alive between groups at a point in time (Table 2). However, the impact of framing differed substantially between Caucasian and non-Caucasian ($P = 0.0004$ for test of interaction) and between subjects with more or less than a high school education ($P = 0.002$ for test of interaction) (Tables 3 and 4). For example, for Caucasians, the difference in the proportion of respondents answering correctly between the survival and mortality frames was only 6%, whereas for non-Caucasians the difference between the 2 frames was 26%. Similarly, for participants with more than a high school education, the difference in the proportion of respondents answering correctly between the survival and mortality frames was only 7%, whereas for participants with less than a high school education the difference between the 2 frames was 27%. We present results on the combined effects of education and ethnicity in Table 5. Although education and ethnicity were correlated in our study population, education and ethnicity also have independent effects on the impact of framing on understanding, with the greatest impact of framing among participants who had less than a college education and were non-Caucasian. After adjusting for age, gender, education, and ethnicity, the interactions between ethnicity and framing and between education and framing remained statistically significant ($P = 0.04$ and $P = 0.007$, respectively). Because our study was not powered to examine framing effects within the subgroups identified in Table 5, we did not test for framing effects within each subgroup. The impact of framing did not differ by gender or age of participants ($P > 0.6$).

EFFECT OF FRAMING ON CHOICE

Participants who received the information framed only as survival curves were more likely to choose to undergo preventive surgery than participants who received the information framed as mortality curves only (Table 2). Participants who received the information framed as both survival and mortality curves were less likely to choose preventive surgery than participants

Table 2 Effect of Framing on Understanding and Treatment Preference

	Mortality Curve	Both Curves	Survival Curve	*P* Value for Trend
Proportion of participants answering accurately				
Number alive (dead) in 1 group	0.54[a]	0.67[b]	0.69[b]	0.01
Which group has more alive (dead)	0.75[a]	0.84[a,b]	0.85[b]	0.05
Difference in number alive (dead) between groups	0.43[a]	0.49[a,b]	0.56[b]	0.03
All understanding questions	0.38[a]	0.48[a,b]	0.52[b]	0.02
Proportion of participants choosing colectomy				
5% increase in survival	0.39[a]	0.51[b]	0.55[b]	0.02
10% increase in survival	0.51[a]	0.56[a]	0.59[a]	0.35
20% increase in survival	0.53[a]	0.62[a,b]	0.70[b]	0.06

Note: Cells within a row that share a superscript are not statistically different at $P = 0.05$.

Table 3 Effect of Framing on Understanding According to Ethnicity

	Proportion of Participants Answering Accurately		
	Mortality	**Both**	**Survival**
Overall	0.38[a]	0.48[a,b]	0.52[b]
Caucasian (n = 213)	0.63[a]	0.70[a]	0.57[a]
Non-Caucasian (n = 213)	0.14[a]	0.34[b]	0.40[b]

Table 4 Effect of Framing on Understanding According to Education

	Proportion of Participants Answering Accurately		
	Mortality	**Both**	**Survival**
Overall	0.38[a]	0.48[a,b]	0.52[b]
More than high school (n = 251)	0.64[a]	0.62[a]	0.57[a]
High school or less (n = 180)	0.09[a]	0.35[b]	0.36[b]

Note: Cells within a row that share a superscript are not statistically different at $P = 0.05$.

receiving survival curves only and more likely to choose preventive surgery than participants receiving mortality curves only. This pattern was consistent across the 3 levels of benefit tested. However, the test for trend was only significant at $P < 0.05$ for the scenario in which colectomy increased survival by 5%. Overall, subject preferences were transitively ordered for all 3 ways of framing the information, with a greater proportion of participants choosing preventive surgery as the benefit of the surgery increased.

The effect of framing on preference for surgery was not modified by the participants' ethnicity (Caucasian vs. non-Caucasian), education, gender, or age. For the graph in which colectomy provided a 10% increase in survival, there was a trend toward a greater effect of framing on preference among individuals who answered all the understanding questions correctly (interaction $P = 0.13$). However, this trend was not seen in the graphs where colectomy provided a 5% or 20% increase in survival (interaction $P > 0.5$).

Discussion

The results of this study suggest that framing of information about risk over time as survival versus mortality curves can affect understanding and treatment preferences. Presenting information as mortality curves resulted in lower levels of understanding and fewer participants' choosing preventive colectomy than presenting information as survival curves. Presenting information in both frames (i.e., showing both survival and mortality curves) resulted in levels of understanding and preference for preventive colectomy between presentation of survival curves only and presentation of mortality curves only, but was not statistically different from presenting information as survival curves only.

The impact of gain versus loss framing on choice is most often associated with prospect theory. However, prospect theory was developed primarily to explain choices between risky and riskless options. Typically, in such risky choice framing effects, people prefer risky options when choices are negatively framed and certain outcomes when they are positively framed. Levin et al.[15] distinguished this type of framing effect from 2 others: attribute framing and goal framing. In attribute framing, people are not asked to choose between independent options; instead, they are asked to evaluate a single item. Their evaluation depends on whether a specific attribute of that item is positively or negatively framed. For example, people's attitudes toward the quality of ground beef depend on whether the beef is labeled as 75% lean or 25% fat. In goal framing, people are asked to pursue a specific goal, with the importance of the goal framed either as the positive consequences

Table 5 Effect of Framing on Understanding According to Ethnicity and Education

	Proportion of Participants Answering Accurately		
	Mortality	**Both**	**Survival**
Overall	0.38	0.48	0.52
Caucasian, more than high school (n = 141)	0.80	0.77	0.66
Caucasian, less than high school (n = 72)	0.23	0.56	0.44
Non-Caucasian, more than high school (n = 106)	0.32	0.44	0.50
Non-Caucasian, less than high school (n = 107)	0.02	0.15	0.30

of performing the act or the negative conse-quences of not performing the act. For example, women were more apt to engage in breast self-examination when presented with information stressing the negative consequences of not engaging in such examinations than when presented with information stressing the positive consequences of engaging in such examinations. Across all 3 of these framing effects, people's choices or evaluations have been shown to vary depending on whether the situation is positively or negatively framed. However, the effect of the framing manipulation on choice and evaluation depends on which of the 3 framing effects is at play.

The survival and mortality curves in our study are not clear examples of any of these types of framing effects. Unlike risky choice framing effects, neither of our options was riskless. Unlike attribute framing, we did not ask people to make mere evaluations; rather, we asked them to choose between 2 options. Unlike goal framing, we did not ask people to pursue some goal; rather, we asked them to make a choice. In fact, survival and mortality curves represent an interesting new context in which to study framing effects. They have unique features that deserve to be studied. For example, survival curves present the number of people alive at any point in time. This is a positive way of framing the information. But survival curves represent this number graphically as a loss, that is, a decrease from 100% survival. Similarly, mortality curves present the number of people dead at any given time, a negative framing. However, they represent this number graphically as a gain, that is, an increase from 0% mortality.

The complexity of the framing effect created by survival curves is better illustrated by comparing it to simpler ways of presenting people with medical choices. Suppose, for example, people are asked to decide whether they want to undergo a surgery that has a 95% survival rate. Consistent with attribute framing effects that have been found, it would be expected that they would view this surgery more positively than a surgery they were told had a 5% mortality rate. This type of framing effect is quite predictable and relatively well understood. By contrast, in our study, we presented people with 2 curves, illustrating survival (or mortality) rates for surgery versus no surgery. Presenting this information in terms of survival curves potentially makes both surgery and going without surgery more attractive because both options would be described in terms of the number of people surviving. It is not at all clear how this framing of the information would change the relative desirability of the 2 options. Similarly, when looking at survival curves of these 2 options, people might focus on how many more patients are alive who underwent surgery. By contrast, with mortality curves, people might focus on how many more patients are dead who did not receive surgery.

There is another reason that the framing effects created by survival and mortality curves in this study are difficult to categorize: The psychophysical space between the 2 treatment options differs across the 2 types of curves. Consider the outcomes 50 years after the decision. In the survival curve, surgery increases absolute survival from 40% to 50%, a relative gain of 25%. In the mortality curves, it reduces mortality from 60% to 50%, a 16.7% relative reduction. Future research should focus on trying to tease apart what people attend to when viewing survival or mortality curves.

Most studies of the impact of gain versus loss framing have used information about outcomes at a single point in time (e.g., risk of death with treatment A vs. risk of survival with treatment A).[5–7,9,16,17] These studies have been unable to examine the effect of framing on understanding beyond the ability to repeat the single piece of risk information provided. Because survival and mortality curves contain extensive information about risk over time, they allowed us to assess the impact of gain versus loss framing on more wide-ranging measures of understanding. In this study, presentation of information as mortality curves resulted in significantly lower levels of understanding (as measured by answers to questions about the information) than presentation of information as survival curves. This framing effect appeared to be greatest among individuals with less education or minority race. Although the reason for this difference is not clear from the current study, it is interesting to speculate that the greater difficulty in answering questions about loss may suggest that participants are more averse to thinking in terms of loss, more confused by mortality curves because a rise in the curve signifies a greater loss (i.e., more people dying), or more familiar with the term "survival" than the term "mortality." Furthermore, these factors may be more common among less educated participants, explaining the interaction with educational level. Practically, however, this finding suggests that care must be taken in assuming that information framed as gain or loss is equally well understood among subjects from different backgrounds. Framing information as a loss may result in both less interest in an intervention and lower levels of understanding.

Although presentation of both gain and loss framing is often proposed as the best way to resolve the bias created by presentation using either frame alone, our study provides some of the first empirical evidence about the outcomes of such a strategy.[10,11] In this study, presentation of both survival and mortality curves re-

sulted in preferences and understanding in between those seen with the presentation of either frame alone, although not statistically different from preferences with survival curves only. Further studies with greater power to measure relatively small differences in preference between groups are needed to determine whether the trend toward the use of both frames to unbias the presentation seen in this study represents a real effect.

This study has several limitations. Although the juror pool is highly representative of the population of the city of Philadelphia, it is less representative of other segments of the U.S. population. We chose to use jurors rather than patients because of concerns about patients misinterpreting the data from the hypothetical situations as reflections of their own health status. Because of the nature of our experimental study design, we were able to compare only 3 alternative formats of our questionnaire. Clearly, the format of each part of the questionnaire from the introduction to the outcome questions may affect the results. Our results are not necessarily generalizable to other formats.

Involving patients in medical decisions requires effective communication of information about the risks and benefits of alternative choices. Presentation of information using survival or mortality (i.e., incidence) curves offers a potentially powerful method of communication in this setting because such curves provide extensive information about risk over time in a relatively simple graphic format. However, presentation of either survival or mortality curves alone can result in an effect of framing on understanding and treatment preference.

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BRIEF REPORT

Using Survival Curve Comparisons to Inform Patient Decision Making

Can a Practice Exercise Improve Understanding?

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BACKGROUND: **Patients often face medical decisions that involve outcomes that occur and change over time. Survival curves are a promising communication tool for patient decision support because they present information about the probability of an outcome over time in a simple graphic format. However, previous studies of survival curves did not measure comprehension, used face-to-face explanations, and focused on a VA population.**

METHODS: **In this study, 246 individuals awaiting jury duty at the Philadelphia County Courthouse were randomized to receive one of two questionnaires. The control group received a questionnaire describing two hypothetical treatments and a graph with two survival curves showing the outcomes of each treatment. The practice group received the same questionnaire preceded by a practice exercise asking questions about a graph containing a single curve. Subjects' ability to interpret survival from a curve and ability to calculate change in survival over time were measured.**

RESULTS: **Understanding of survival at a single point in time from a graph containing two survival curves was high overall, and was improved by the use of a single curve practice exercise. With a practice exercise, subjects were over 80% accurate in interpreting survival at a single point in time. Understanding of changes in survival over time was lower overall, and was not improved by the use of a practice exercise. With or without a practice exercise, subjects were only 55% accurate in calculating changes in survival.**

CONCLUSION: **The majority of the general public can interpret survival at a point in time from self-administered survival curves. This understanding is improved by a single curve practice exercise. However, a significant proportion of the general public cannot calculate change in survival over time. Further research is necessary to determine the effectiveness of survival curves in improving risk communication and patient decision making.**

KEY WORDS: **decision making; communication; patient education.**

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Patients often face medical decisions involving outcomes that occur and change over time. Choosing an aggressive treatment over a less aggressive treatment may trade short-term increase in mortality for long-term increase in survival. In many situations, a patient must understand both the conditional probabilities of an outcome and how those probabilities change over time. Although it is well established that patients want to receive risk information, how best to present this complex information is not clear.[1] Extensive numerical information may overwhelm a patient's ability to process and understand it.[2,3] However, presenting limited information, for example, survival probabilities at two or three time points, may bias decisions.[4,5]

Survival curves may overcome these problems by presenting information about the probability of an outcome over time in a simple graphic format without extensive numeric data. Several studies have used survival curves to convey information about treatment choices to patients in face-to-face discussions.[6–9] We have chosen to extend this research for several reasons. First, recent literature suggests patients may have difficulty understanding even simple probabilities.[10] Prior studies did not measure subjects' ability to understand survival curve information. Second, because many decision aids being developed are self-administered, it is important to establish whether patients can understand self-administered survival curves.[11,12] Finally, participants for prior studies came from Veterans' Administration (VA) clinics and may not be generalizable to other patient populations.

Using survival curves to aid decision making involves making comparisons between multiple curves. Although a survival curve is a relatively simple method of presenting complex information, a graph containing multiple survival curves may appear sufficiently complex to be overwhelming. The ability to perform many cognitive tasks is dependent on the development of cognitive rules or heuristics.[3,13] For survival curve understanding, we hypothesized that these rules would be more easily developed on a relatively more simple graph containing a single curve, and, thus, presenting individuals with a graph containing a single curve prior

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to a graph containing multiple curves would improve understanding of the more complex, multiple curve graph.

The objectives of our study were to determine: 1) if the general public can understand survival curves when presented in a self-administered format; and 2) if understanding of a graph containing a two-curve comparison improves with a single curve practice exercise.

METHODS

Study Design

We randomized study subjects to receive one of two questionnaires. The control group received a questionnaire describing a hypothetical health condition with two possible treatments and a graph with two survival curves showing the outcomes of the treatments. The practice group received the same questionnaire preceded by a practice exercise asking questions about a graph containing a single curve. The study protocol was approved by the Human Subjects Committee of the Institutional Review Board at the University of Pennsylvania.

Study Setting and Participants

Prospective jurors awaiting jury selection at the Philadelphia County Courthouse were offered a candy bar to complete the study questionnaire. The two versions of the questionnaire were randomly ordered and distributed sequentially to volunteers. Based on our prior experience, we estimated that approximately 75% of prospective jurors volunteer to participate and over 90% of individuals who volunteer complete the questionnaires. In Philadelphia, individuals are randomly selected for jury duty from voter registration and drivers license records.

Intervention

Each participant received a self-administered questionnaire that included a brief explanation of survival curves and a graph containing two survival curves illustrating the outcomes of two hypothetical treatments and outcome measurement questions (see below) (Appendix A). The brief explanation read:

> *We will show you a graph of survival curves. A survival curve is a picture that shows how long people live after being diagnosed with a disease. You will notice there are different curves on the graph. Each curve shows how many people survive using the different treatments for a disease. Survival curves are shown to patients to help them understand their disease and to decide which treatment option is best for them.*

A brief explanation of the graph was provided below the two curve graph:

> *The graph above shows how many people survive after either having surgery or being put on medication for an imaginary disease called Soap-operatitis. At year 0, 100 patients were started on Soap-operatitis medication and 100 patients had Soap-operatitis surgery. The curve marked by the squares shows the patients who had surgery. The curve marked by the circles shows the patients who are on medication. The curves show how many people are alive every five years after having surgery or being put on medication.*

For participants randomized to the practice arm, the questionnaire began with an additional page containing a practice exercise with a single survival curve for a hypothetical condition and several questions about the information contained in the curve (Appendix B). The correct answers to these questions were not provided.

Outcome Measures

The primary outcome measure was comprehension of the information contained in the figure containing two survival curves. Subjects both interpreted survival rates at a single time point (e.g., How many people having surgery are alive at year 20?) and change in survival over a specific time period (e.g., How many people having surgery died between year 20 and year 40?). Answers were considered correct only if they exactly matched the correct answer. Answers left blank were considered missing data, rather than incorrect answers.

Statistical Analysis

Baseline characteristics of the two groups were compared using χ^2 tests for categorical variables and t tests for continuous variables. For each subject, separate accuracy scores were generated for the ability to interpret the number alive at a given point (five questions) and the ability to calculate change in survival (two questions), by dividing the number of questions answered correctly by the total number of questions. Because these scores were not normally distributed, they were compared between groups using the Mann-Whitney U test. For the practice group, accuracy scores were generated for the single curve graph and compared within subject to their accuracy scores for the double curve graph using the Wilcoxon signed rank test.

RESULTS

Of the 246 subjects who completed the questionnaire, 120 received the practice intervention and 126 did not. The two groups were similar in age, gender, education, and ethnicity (Table 1).

Table 1. Subject Characteristics

	Practice Exercise	Control	*P* Value
Mean age (±SD)	39.7(12.4)	39.9(12.7)	.88
Women, %	68	66	.82
Caucasian, %	55	47	.24
African American, %	40	44	.12
Mean years of education (range ± SD)	13.8(2.2)	14.0(2.2)	.78

Table 2. Comprehension of Double Curve Presentation

	Practice Exercise	Control	*P* Value
% Correctly identifying number of survivors at a single point	83	74	.03
% Correctly identifying change in number of survivors between two time points	55	55	.89

Understanding of survival at a single point in time from a graph containing two survival curves was high overall and improved with a single curve practice exercise (Table 2). With a practice exercise, subjects were over eighty percent accurate in interpreting survival at a single point in time. Furthermore, two thirds of subjects (66%) answered all of these questions correctly and an additional 14% answered all but one question correctly. Understanding of changes in survival over time was lower overall, and was not improved by the use of a practice exercise (Table 2). With or without a practice exercise, subjects were only 55% accurate in calculating change in survival. Furthermore, only 54% of subjects answered over half of these questions correctly, and 33% were unable to answer any question correctly. Mean accuracy scores did not differ significantly by gender, educational level, or ethnicity (all $P > .10$).

Among individuals receiving a single curve practice exercise, understanding of the graph containing a single curve was greater than understanding of the graph containing two curves. The great majority of errors in interpreting survival or calculating change in survival were large in magnitude. For example, accuracy in interpreting the number of people alive at a point in time declined from 92% in the single curve graph to 83% in the double curve graph ($P = .006$), and accuracy in calculating change in survival over time declined from 67% to 55% ($P = .04$).

DISCUSSION

Our results suggest that the majority of the general public can understand survival at a point in time from a graph comparing two survival curves and that this understanding is improved by a single curve practice exercise. However, almost half of our subjects could not calculate a change in survival over time from a survival curve — a task that requires subjects to correctly estimate the number of people surviving at two time points and to accurately subtract those two numbers.

Prior studies have used survival curves to demonstrate that patients focus on different portions of survival curves than physicians, that order of presentation affects treatment preferences, that length of the explanation affects treatment preferences and that patients are willing to trade a short term increase in mortality for long term increase in survival.[5–8] To our knowledge, our study is the first to demonstrate that the general public can calculate survival from a survival curve even without a face-to-face explanation. Importantly, however, our study raises significant concerns about the ability of the general public to calculate differences in survival from a survival curve. Such comparisons may be an important component of the cognitive tasks necessary for patients to use survival curve information to aid their decision making.

Our study has several limitations. Although the juror pool is highly representative of the Philadelphia population, it is less representative of other segments of the U.S. population. Second, we compared only two formats of our questionnaire. The format of each part of the questionnaire may affect the results. Our results are not necessarily generalizable to other formats. Third, because the instructions on the questionnaire were written at a ninth-grade reading level and in relatively small font, it is possible that they were not understood by some participants.

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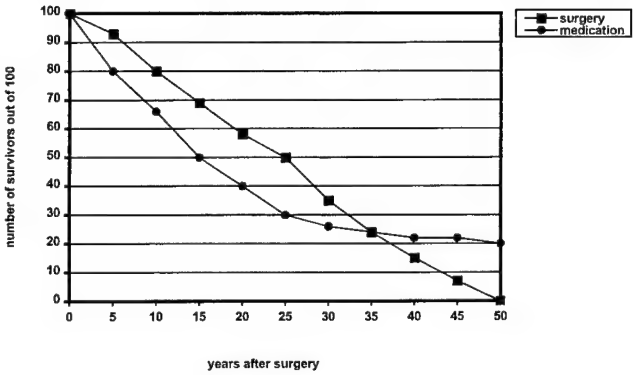
APPENDIX A

Double Curve Graph

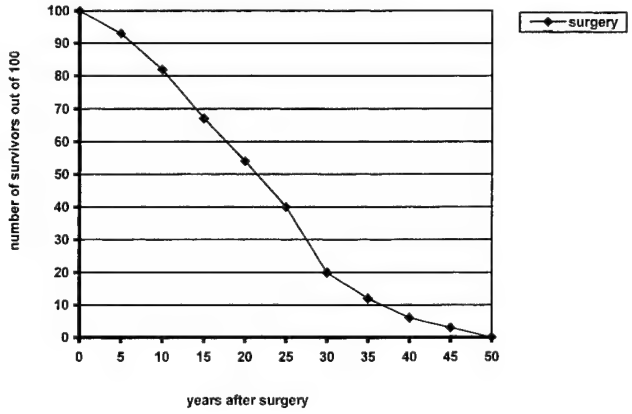


The graph above shows how many people survive after either having surgery or being put on medication for an imaginary disease called Soap-operatitis. At year 0, 100 patients were started on Soap-operatitis medication and 100 patients had Soap-operatitis surgery. The curve marked by the squares shows the patients who had surgery. The curve marked by the circles shows the patients who are on medication. The graphs show how many people are alive every five years after having surgery or being put on medication.

1. How many people are alive at year 0 who are on medication? _____
2. How many people are alive at year 0 who have surgery? _____
3. How many people are alive at year 15 after receiving medication? _____
4. How many people are alive at year 20 after having surgery? _____
5. How many people are alive at year 25 after having surgery? _____
6. How many people on medication died between years 5 and 15? _____
7. How many people died after having surgery between years 20 and 25? _____
8. Which treatment would you choose? _____

APPENDIX B

Single Curve Practice Exercise



The above graph shows the number of people who survive after having surgery for a disease called Chocalitis. It begins with 100 patients having surgery at year 0. The graph shows how many people are alive every five years after having surgery. For example, twenty years after surgery, 54 people are still alive. Please answer the following questions using the above graph.

1. How many people are alive at year 0? _____
2. How many people are alive at year 25? _____
3. How many people died between year 0 and year 30? _____
4. How many people are alive at year 50? _____
5. Did more people die between years 0 and 5 or between years 10 and 15? _____

REVIEW

The Challenge of Problem Residents

David C. Yao, MD, MPH, Scott M. Wright, MD

Internal medicine residency training is demanding and residents can experience a wide variety of professional and personal difficulties. Residency programs everywhere have had and will continue to have problem residents. Training programs should be equipped to effectively identify and manage residents who experience problems. Previous articles that have been published on the topic of problem residents primarily addressed concerns such as impairment due to depression and substance abuse. The content of this article is derived from a comprehensive review of the literature as well as other data sources such as interviews with program directors and workshops at national professional meetings. This article focuses primarily on four issues related to problem residents: their identification, underlying causes, management, and prevention. The study attempts to be evidence-based, wherever possible, highlighting what is known. Recommendations based on the synthesis of the data are also made. Future ongoing studies of problem residents will improve our understanding of the matters involved, and may ultimately lead to improved outcomes for these trainees.

KEY WORDS: **medical education; internship; residency; problem resident.**
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The American Board of Internal Medicine (ABIM) defines a problem resident as "a trainee who demonstrates a significant enough problem that requires intervention by someone of authority, usually the program director or chief resident."[1] Problem residents are ubiquitous (present in 94% of internal medicine residency programs during the academic year 1998–1999) and are moderately prevalent (7% of internal medicine residency trainees).[2] They can be found in all types of residency training programs—large and small, community-based and university-affiliated, psychiatric and surgical. Problem residents are challenging to the residency program directors, attending physicians, and often their fellow trainees. They can threaten the integrity of a training program and can negatively influence the residency training experience for other trainees.[3–5]

The goal of an internal medicine residency program is to train and prepare newly graduated medical students to become competent internists. Since 1972, the ABIM has relied on residency programs to evaluate the readiness of eligible candidates for certification. Accordingly, attempts have been made to standardize resident evaluation at the program level. After the identification of a problem resident, program directors often have to help facilitate the successful remedy of the problem in order to recommend the resident for promotion, graduation, and certification.

This report may help to provide a better understanding of the issues related to problem residents, thereby supporting residency program directors, medical educators, and residents themselves. This article reviews the literature, and provides perspectives and recommendations from other sources to comprehensively examine four vital issues related to problem residents: identification, underlying causes, management, and prevention.

METHODS

Literature Search

Databases, including MEDLINE (years 1966–2000), PsychINFO (1977–2000), ERIC (1966–1999), and HealthSTAR (1975–2000), were searched using and combining the MeSH terms "Internship and Residency" and "Medical-Residency" with (1)"Drug Abuse/Addiction/Dependency/Usage," "Alcohol Abuse/Alcoholism" (yield, 27 articles), (2) "Stress," "Occupational Stress," "Stress Management," "Coping Behavior" (yield, 109 articles), and (3) "Behavior Problems," "Psychological Phenomena," "Mental Disorder," "Depression," and "Affective Disturbances" (yield, 101 articles). A search of these databases for articles containing the textword "problem resident" or "resident in difficulty" was also performed. The bibliographies of the retrieved articles were also examined for relevant articles. Abstracts of articles were reviewed and selection criteria included English language and studies involving issues related to resident welfare. Excluded were editorials and studies reporting on residencies outside of North America.

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Cost-Effectiveness of Raloxifene and Hormone Replacement Therapy in Postmenopausal Women: Impact of Breast Cancer Risk

Katrina Armstrong, MD, MSc, Tze-Ming Chen, MD, Daniel Albert, MD, Thomas C. Randall, MD, and J. Sanford Schwartz, MD

OBJECTIVE: To examine the life expectancy and cost-effectiveness of hormone replacement therapy (HRT) and raloxifene therapy in healthy 50-year-old postmenopausal women.

METHODS: We performed a cost-effectiveness analysis using a Markov model, discounting the value of future costs and benefits to account for their time of occurrence.

RESULTS: Both HRT and raloxifene therapy increase life expectancy and are cost-effective relative to no therapy for 50-year-old postmenopausal women. For women at average breast cancer and coronary heart disease risk, lifetime HRT increases quality-adjusted life expectancy more (1.75 versus 1.32 quality-adjusted life years) and costs less ($3802 versus $12,968) than lifetime raloxifene therapy. However, raloxifene is more cost-effective than HRT for women at average coronary risk who have a lifetime breast cancer risk of 15% or higher or who receive 10 years or less of postmenopausal therapy. Raloxifene is also the more cost-effective alternative if HRT reduces coronary heart disease risk by less than 20%.

CONCLUSIONS: Assuming the benefit of HRT in coronary heart disease prevention from observational studies, long-term HRT is the most cost-effective alternative for women at average breast cancer and coronary heart disease risk seeking to extend their quality-adjusted life expectancy after menopause. However, raloxifene is the more cost-effective alternative for women at average coronary risk with one or more major breast cancer risk factors (first-degree relative, prior breast biopsy, atypical hyperplasia or *BRCA1/2* mutation). These results can help inform decisions about postmenopausal therapy until the results of large scale randomized trials of these therapies become available. (Obstet Gynecol 2001;98:996–1003. © 2001 by the American College of Obstetricians and Gynecologists.)

Deciding about the use of hormone replacement therapy (HRT) or raloxifene after menopause is difficult. These therapies have multiple, often competing effects.[1–7] The most effective method of extending life expectancy depends upon an individual woman's risk for osteoporotic fracture, coronary heart disease, or breast cancer, and the relative efficacy of these therapies on reducing these events. Synthesizing this complex information is made particularly difficult by the large number of often conflicting studies and the need to extrapolate the efficacy of raloxifene on clinical outcomes from surrogate endpoints and the efficacy of HRT from observational studies.[5,6,8] Furthermore, differences in prescription drug costs of raloxifene therapy and HRT suggest that the short- and long-term economic costs of these therapies may vary substantially.

In this setting, decision analysis offers a systematic approach to evaluating the comparative clinical and cost-effectiveness of alternative therapies, including the impact of alternative assumptions on outcomes of interest. The objective of the present study was to examine the life expectancy and cost-effectiveness of HRT and raloxifene therapy to prevent the long-term complications of estrogen deficiency among healthy postmenopausal women.

MATERIALS AND METHODS

Clinical and cost-effectiveness were estimated using a time-dependent Markov model that simulated the out-

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Table 1. Disease Incidence and Mortality

		Sensitivity analysis range	Source(s) (references)
Coronary heart disease			
Incidence	0.32 lifetime	0.30–0.90	11, 12
Mortality	0.1–0.3 first y	0.05–0.4	14, 15
	0.01–0.04 subsequent y	0.005–0.02	
Hip fracture			
Incidence	0.14 lifetime	0.10–0.40	25
Mortality	0.17 first y	0.08–0.35	26
Vertebral fracture			
Incidence	0.18 lifetime	0.04–0.20	27
Mortality			
Breast cancer			
Incidence	0.10 lifetime	0.05–0.50	28
Mortality	0.025 first y	0.01–0.05	28
	0.032 subsequent y	0.01–0.05	
Endometrial cancer			
Incidence	0.026 lifetime	0.01–0.05	28
Mortality	0.15 first y	0.05–0.3	28
Thromboembolism			
Incidence	0.00072 annually	0.0003–0.002	4
Mortality	0.016 first y	0.008–0.03	29

comes of HRT, raloxifene, or no therapy in hypothetical cohorts of 50-year-old healthy postmenopausal women. The simulation included the six major outcomes affected by raloxifene and HRT: coronary heart disease, vertebral fracture, hip fracture, thromboembolism, endometrial cancer, and breast cancer. Because data about the impact of HRT on colon cancer and Alzheimer's disease are preliminary and corresponding data are not available for raloxifene, these outcomes were not included in the simulation. Risks of developing each outcome were independent of prior outcomes. The simulation was run until all cohort members died or reached age 101.

The analysis compared three alternative regimens: HRT (0.625 mg of oral conjugated estrogen per day with cyclic progestin for 10–14 days per month in women with an intact uterus); raloxifene (60 mg per day); and no treatment. All women were assumed to be compliant with therapy. The base-case analysis examined use of continuous therapy from age 50 until death. Because some women take HRT or raloxifene for shorter time periods, therapy of 5- and 10-years duration after menopause at age 50 was examined in secondary analyses, with benefits of therapy assumed to continue only while therapy was used.

Simulation outcomes included life expectancy, quality-adjusted life years, and direct medical cost.[9] Although the inclusion of all direct medical costs is consistent with a societal perspective, nonhealth effects, health effects on people other than the woman in question, indirect medical costs and nonmedical costs are not currently able to be measured adequately and were not included in the analysis.[9] Costs and benefits were discounted at a 3% annual rate to account for their decreased value over time.[9] The model was validated by comparing the life expectancy of a 50-year-old woman at average cardiac and breast cancer risk who selects no therapy from the simulation (31.68 years) to estimated life expectancy of a 50-year-old US woman from the National Center for Health Statistics (31.7 years).[10]

Transition probabilities for disease incidence, disease mortality, and the impact of alternative therapies on disease incidence are shown in Tables 1 and 2. For the base-case analysis, the probability of developing coronary heart disease was that of women with population levels of low-density lipoprotein, total cholesterol, systolic blood pressure, no history of diabetes, smoking, or left ventricular hypertrophy.[11,12] The effect of raloxifene on coronary heart disease was estimated from its impact on total cholesterol and high-density lipoprotein in the base-case analysis and its impact on low-density lipoprotein in sensitivity analyses.[12,13] The effect of HRT on coronary heart disease was taken from a large, prospective cohort study in the base-case and its impact on lipids in sensitivity analyses.[1,13] Consistent with the results of a recent randomized controlled trial of HRT in women with coronary heart disease (HERS), HRT was assumed not to affect mortality after a diagnosis of coronary heart disease.[8] Estimated mortality after a diagnosis of coronary heart disease was adjusted for the recent substantial decrease in coronary heart disease case fatality among US women.[14,15]

The relative risk of hip fracture in the base-case anal-

Table 2. Effect of Interventions on Disease Incidence

	Relative risk	Sensitivity analysis range	Source(s) (references)
HRT			
Coronary heart disease	0.56	0.3–1.0	1
Hip fracture	0.53	0.3–1.0	2
Vertebral fracture	0.53	0.3–1.0	2
Breast cancer	1.35	1.0–2.0	3
Endometrial cancer	1.00	1.0–6.0	30
Thromboembolism	2.10	1.0–7.8	29
Raloxifene			
Coronary heart disease	0.87	0.5–1.0	5, 6
Hip fracture	0.93	0.5–1.0	5
Vertebral fracture	0.67	0.5–1.0	7
Breast cancer	0.24	0.1–1.0	4
Endometrial cancer	1.00	1.0–6.0	4
Thromboembolism	3.10	1.0–6.2	4

HRT = hormone replacement therapy.

ysis was determined from the effect of raloxifene on bone mineral density, and the point estimate from the MORE study was examined in sensitivity analyses.[4,5] Vertebral fractures were assumed to affect costs and quality of life but not life expectancy. The effect of HRT on vertebral fracture was assumed to be equal to its effect on hip fractures. Although HRT was assumed not to increase the risk of endometrial cancer in the base-case analysis, increases in endometrial cancer risk were examined in sensitivity analyses. Mortality from other causes was obtained by subtracting mortality from the outcomes included in the model from all-cause mortality rates.[10]

Cost and utility model parameters are shown in Table 3. Direct medical costs included average wholesale medication acquisition costs for HRT and raloxifene (obtained from the Red Book[16]) and costs of medical care for health outcomes (obtained from the published literature). All costs were adjusted to year 2000 dollars using the medical component of the Consumer Price Index.[17] Quality-adjusted life expectancy was calculated from utility values assigned to each health state in the model by 30 local internists. Because of the limitations of using physician utilities as proxies for patient utilities, sensitivity analyses were conducted using the range of relevant health state patient utilities reported in the literature.[9] Future benefits, events, and costs were adjusted for time effects using a 3% discount rate.[9]

Because of limited randomized trial data and concerns about the generalizability of the data that are available, sensitivity analyses were performed to assess the impact of uncertainty of data inputs and to provide information for women with different risk profiles. One- and two-way sensitivity analyses were conducted to assess the impact of alternative assumptions about: 1) effectiveness of HRT in primary prevention of coronary heart disease; 2) effectiveness of raloxifene in primary prevention of coronary heart disease; 3) magnitude of breast cancer risk associated with HRT; 4) effectiveness of raloxifene in primary prevention of breast cancer; and 5) existence of any residual increase in risk of endometrial cancer with estrogen/progesterone regimens. For each sensitiv-

Table 3. Costs and Utilities

	Costs ($)		Utilities
	Estimate	Source(s) (references)	Estimate
Coronary heart disease			
First y	3690		0.665
Subsequent y	1155	11, 31, 32	0.871
Death	12,995		0.274
Breast cancer			
First y	12,775		0.546
Subsequent y	1400	33	0.864
Death	22,835		0.192
Hip fracture			
First y	18,403		0.613
Subsequent y		34	0.915
Death	20,500		
Vertebral fracture			
First y	4980		0.704
Subsequent y			0.858
Death		35	
Endometrial cancer			
First y	12,724		0.577
Subsequent y	881		0.881
Death	21,265	36	0.192
Thromboembolism			
First y	5790		0.682
Subsequent y		37	0.925
Death	10,085		
Raloxifene (annually)	740	16	
HRT (annually)	270		

Abbreviation as in Table 2.

Table 4. Results

Time frame	Strategy*	Δ LE	Δ QALY	Δ Cost ($)	Incremental CE ($/QALY)
Long-term therapy	**HRT** vs no therapy	0.65	1.75	3802	2173
	Raloxifene vs no therapy	0.71	1.32	12,968	9824
	Raloxifene vs **HRT**	0.06	−0.43	9166	HRT dominant†
5-y therapy	**HRT** vs no therapy	0.16	0.45	2259	5020
	Raloxifene vs no therapy	0.28	0.52	4851	9328
	Raloxifene vs HRT	0.12	0.07	2592	37,029
10-y therapy	**HRT** vs no therapy	0.36	0.90	3834	4260
	Raloxifene vs no therapy	0.47	1.03	8123	7886
	Raloxifene vs HRT	0.11	0.13	4289	32,992

LE = life expectancy; QALY = quality-adjusted life years; CE = cost-effectiveness. Other abbreviation as in Table 2.
* Strategy in bold represents the most cost-effective alternative.
† Both more effective and less costly.

ity analysis, threshold values were identified where alternative regimens exceeded $50,000 per quality-adjusted life year and where alternatives no longer increased life expectancy. The range of values was taken from the widest 95% confidence interval in published studies or from the range of reasonable values developed through discussion with local experts. Because of uncertainty in the measurement of costs and utilities, the range for sensitivity analyses always included estimates from at least half to twice the base-case value.

RESULTS

Compared with no treatment, both lifetime HRT and raloxifene therapy increase life expectancy and quality-adjusted life expectancy and are cost-effective for a 50-year-old postmenopausal woman at average risk for coronary heart disease and breast cancer. HRT provides an additional 0.65 discounted years of life expectancy at a net lifetime discounted cost of $3802 ($5849 per additional year of life); raloxifene an additional 0.71 discounted years of life expectancy at a net lifetime discounted cost of $12,968 ($18,265 per additional year of life) (Table 4). Because HRT reduces hip and vertebral fractures more than raloxifene therapy and fractures impact quality of life more than mortality, HRT increases quality-adjusted life years more than raloxifene therapy (gain of 1.75 versus 1.32 quality-adjusted life years) at a lower cost ($2173 versus $9824 per additional quality-adjusted life year). Thus, when choosing between lifelong raloxifene therapy and HRT, HRT is the dominant alternative (more effective and less costly). However, for shorter durations of therapy (ie, 5 or 10 years after menopause at age 50), raloxifene results in greater increase in life expectancy and quality-adjusted life expectancy than HRT at a cost of less than $50,000 per additional quality-adjusted life year.

As the estimated effectiveness of HRT for primary prevention of coronary heart disease declines, the relative effectiveness and cost-effectiveness of HRT decreases (Table 5). If the effect of HRT on lipid profiles

Table 5. Cost-Effectiveness of Long-Term Therapy According to RR of Coronary Heart Disease With HRT

RR	Strategy*	Δ QALY	Δ Cost ($)	Incremental CE ($/QALY)
0.5	**HRT** vs no therapy	1.92	3668	1909
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs **HRT**	−0.60	9301	HRT dominant†
0.7	**HRT** vs no therapy	1.36	4109	3026
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs **HRT**	−0.04	8860	HRT dominant†
0.9	**HRT** vs no therapy	0.82	4531	5519
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs HRT	0.50	8438	17,002
1.0	**HRT** vs no therapy	0.56	4735	8429
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs HRT	0.76	8234	10,900

RR = relative risk. Other abbreviations as in Tables 2 and 4.
* Strategy in bold represents the most cost-effective alternative.
† Both more effective and less costly.

Table 6. Effect of Predicted Lifetime Breast Cancer Risk on Cost-Effectiveness of Long-Term Therapy

Breast cancer risk	Strategy*	Δ QALYs	Δ Cost ($)	Incremental CE ($/QALY)
10%	**HRT** vs no therapy	1.75	3802	2173
	Raloxifene vs no therapy	1.32	12,968	9825
	Raloxifene vs **HRT**	−0.43	9166	HRT dominant†
15%	**HRT** vs no therapy	1.47	4087	2767
	Raloxifene vs no therapy	1.66	12,294	7406
	Raloxifene vs HRT	0.19	8207	43,056
30%	**HRT** vs no therapy	0.83	4730	5715
	Raloxifene vs no therapy	2.57	10,538	4100
	Raloxifene vs HRT	1.74	5808	3830
65%	HRT vs **no therapy**	0	5434	No therapy dominant†
	Raloxifene vs no therapy	4.02	7641	1900
	Raloxifene vs HRT	4.02	2207	549
80%	HRT vs **no therapy**	−0.19	5536	No therapy dominant†
	Raloxifene vs no therapy	4.43	6777	1530
	Raloxifene vs HRT	4.62	1241	269

Abbreviations as in Tables 2 and 4.

* Strategy in bold represents the most cost-effective alternative.

† Both more effective and less costly.

from the Postmenopausal Estrogen/Progestin Interventions trial is used to estimate its impact on coronary heart disease, HRT decreases coronary heart disease risk by 25% (relative risk [RR] 0.75) and remains more effective and less expensive than raloxifene. If HRT does not reduce coronary heart disease risk, raloxifene becomes the preferred alternative with an incremental cost-effectiveness relative to HRT of $10,900 per quality-adjusted life year.

As the estimated effectiveness of raloxifene for primary prevention of coronary heart disease increases, raloxifene becomes relatively more effective and cost-effective than HRT. If raloxifene reduces coronary heart disease incidence by 30% (RR 0.70), raloxifene and HRT result in an equal gain in quality-adjusted life years. If the effect of raloxifene on coronary heart disease is equal to that estimated in the base-case for HRT (RR 0.5), raloxifene is the more cost-effective alternative.

As the risk of breast cancer from HRT increases, the relative effectiveness and cost-effectiveness of HRT compared with raloxifene decrease. However, HRT is both more effective and less expensive than raloxifene therapy across the range of published estimates (RR 0.9–1.74). If HRT does not increase the risk of breast cancer, use of HRT results in an increase of 0.85 quality-adjusted life years compared with use of raloxifene at a cost saving of $10,900.

As raloxifene becomes more effective in primary prevention of breast cancer, it becomes relatively more effective and cost-effective than HRT. If raloxifene reduces the incidence of breast cancer by 90% (RR 0.1), raloxifene results in a gain in 1.66 quality-adjusted life years compared with no therapy. However, if one assumes coronary heart disease risk reduction from HRT, this gain in quality-adjusted life expectancy is still less than that seen with HRT. If raloxifene is less effective in primary prevention of breast cancer than estimated in the base-case analysis (RR 0.36 or higher), the relative benefit of HRT further increases.

The risk of endometrial cancer from HRT has little substantive effect on the relative benefit of HRT. If HRT increases the risk of endometrial cancer four-fold (RR 4.0), the incremental gain in quality-adjusted life years for HRT compared with raloxifene therapy falls to 0.07, but HRT remains both more effective and less expensive.

The relative benefit of these therapies depends upon a woman's risk of coronary heart disease, osteoporosis, and breast cancer. Because the benefit of HRT in reducing coronary heart disease and osteoporosis risk is believed to be substantially greater than that of raloxifene, HRT remains the more effective and less expensive alternative for women at increased risk of coronary heart disease and osteoporosis. However, increases in breast cancer risk have a significant impact on the relative benefit of raloxifene and HRT (Table 6). If a woman has a 40% increase over the estimated population lifetime breast cancer risk of 10% (ie, lifetime risk of 14%), raloxifene results in an equal gain in quality-adjusted life expectancy as HRT, and HRT is no longer the dominant alternative. If a woman has a 50% increase in breast cancer risk (ie, lifetime breast cancer risk of 15% or higher), raloxifene becomes the more cost-effective alternative.

Variation in the estimates of costs, utilities, and discount rates has little substantive effect on which alternative therapy is preferred. If the cost of raloxifene falls to $175 per year, raloxifene becomes the less costly alternative ($12,496 versus $12,518). However, HRT still results in a greater gain in quality-adjusted life expectancy with an incremental cost-effectiveness ratio of $51 per quality-adjusted life year compared with raloxifene. HRT remains the dominant or cost-effective alternative for a woman at average coronary heart disease and breast cancer risk across the ranges of costs examined for HRT, coronary disease, breast cancer, osteoporosis, endometrial cancer, or thromboembolism. Furthermore, although the relative benefit of HRT decreases as the discount rate decreases, if neither costs nor life years are discounted, HRT remains the preferred option, with an incremental cost-effectiveness ratio of raloxifene compared with HRT of $882,896 per quality-adjusted life year.

Although the relative benefit of HRT decreases as the utility estimates for coronary heart disease and osteoporosis increase and the estimates for breast cancer decrease, HRT remains the dominant or cost-effective alternative across the range of utility estimates examined. Because HRT reduces menopausal symptoms whereas raloxifene does not, and this issue may be particularly relevant for women taking therapy for only 5 or 10 years after menopause, we examined the effect of an improvement in utility with HRT compared with raloxifene for these time frames. For short-term therapy, if the model assumes even modest benefit in quality of life from HRT compared with raloxifene (absolute increase of 2% or higher), HRT is both more effective and less expensive than raloxifene therapy for 5- to 10-year courses of therapy.

DISCUSSION

Because of the availability of alternative hormonally active therapies that differ in their impact on coronary heart disease, breast cancer, and osteoporotic fracture, and increasing controversy about the effects of HRT on coronary heart disease, we performed a decision analysis to estimate the clinical (life expectancy and quality-adjusted life expectancy) and economic (incremental cost-effectiveness) impact of HRT and raloxifene in postmenopausal women. Assuming the benefit of HRT on coronary risk reported in observational studies and the benefit of raloxifene on coronary risk extrapolated from its effects on lipids, both long-term HRT and long-term raloxifene increase both life expectancy and quality-adjusted life expectancy in 50-year-old postmenopausal women at average risk for coronary heart disease and breast cancer. Because HRT increases quality-adjusted life expectancy more than raloxifene, and raloxifene is more costly than HRT, HRT is the dominant (more effective and less costly) alternative in this setting. Thus, despite raloxifene's apparent reduction in breast cancer incidence, long-term HRT remains the most cost-effective therapy for women at average breast cancer risk seeking treatment to increase their quality-adjusted life expectancy after menopause.

The relative benefits of raloxifene and HRT depend upon a woman's breast cancer risk. For a woman with a predicted lifetime 50% increase in breast cancer risk (ie, lifetime risk of 15% or higher), raloxifene is a cost-effective alternative to HRT, resulting in a greater increase in quality-adjusted life expectancy at an incremental cost of less than $50,000 per quality-adjusted life year. The most widely used and validated model for individual breast cancer risk prediction is the Gail model.[18,19] Gail model software can be obtained from the National Cancer Institute at 1-800-4CANCER or http://cancertrials.nci.nih.gov/forms/CtRiskDisk.html. If using a software program is not feasible, certain breast cancer risk factors (one or more first-degree relatives with breast cancer, one or more prior breast biopsies, history of atypical hyperplasia on a breast biopsy, and carrying a mutation in *BRCA1* or *BRCA2*) consistently convey an RR of breast cancer over 1.5 and can be used to identify women who have a 15% or greater lifetime risk of breast cancer.[19]

The relative benefits of raloxifene and HRT also change significantly with alternative assumptions about the effects of HRT on coronary heart disease risk. If HRT proves to reduce the risk of a first coronary heart disease event by less than 20%, long-term raloxifene becomes the more cost-effective alternative for all women. If the effects of both HRT and raloxifene are extrapolated from changes in lipids, HRT remains the more cost-effective alternative.[5,13] These results provide evidence to help clinicians interpret and implement recent American Heart Association guidelines that suggest decisions about HRT in women without cardiovascular disease "should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference."[20]

For women interested in pharmacologic therapy for 5 or 10 years after menopause, raloxifene is associated with a greater increase in life expectancy and quality-adjusted life expectancy than HRT at a cost of less than $50,000 per quality-adjusted life year. A woman's risk of death from breast cancer compared with her risk of death from coronary disease and osteoporosis is relatively greater at younger than older ages. Thus, raloxifene's reduction of breast cancer risk has its greatest impact in the years immediately after menopause. How-

ever, the beneficial effect of HRT on menopausal symptoms was not included in this analysis. Even a relatively small symptomatic benefit of HRT relative to raloxifene results in a greater increase in quality-adjusted life years with short-term HRT than with short-term raloxifene.

These results extend prior research in this area. Previous decision analyses without discounting have found HRT to increase life expectancy by 0.5 to 1 year in average-risk women.[21–24] In this analysis, HRT increased life expectancy by 1.0 years in the absence of discounting. One cost-effectiveness analysis also found HRT to be cost-effective compared with no therapy.[21] A recently published decision analysis of alendronate, raloxifene, and HRT found that raloxifene increased life expectancy more than HRT for women at high breast cancer risk and low coronary heart disease risk.[24] However, this prior analysis did not include the recent data about the benefit of raloxifene on breast cancer risk in the base-case analysis or the effects of raloxifene and HRT on vertebral fractures or thrombosis. Furthermore, the current study is the first to assess the comparative economic impact of alternative therapies.

The current study has several limitations. We chose to focus on hormonally active options for postmenopausal women because these options have many competing effects, making a decision analysis particularly valuable. We did not include the many other options for prevention of osteoporosis, coronary disease, and breast cancer that have a single main effect (eg, statins, alendronate), and that may be even more effective than either HRT or raloxifene for a specific complication of hormonal deficiency. However, deciding between options for prevention of a single disorder is potentially less complex, and including all options would make the current analysis difficult to use. Because both HRT and raloxifene have side effects, and an extensive literature search found no evidence that patient adherence differs between the therapies, we did not include the effects of noncompliance in the model. In addition, for many of the model parameters, only limited data are currently available. For example, data on the impact of raloxifene on breast and endometrial cancer come from a single large clinical trial.[4] Although we used the best available evidence for each model parameter estimate, uncertainty is inevitable (eg, effect of HRT on coronary heart disease). In this setting, sensitivity analyses were used to understand the impact of the ranges of uncertainty and provide an important context for understanding the base-case results.

Postmenopausal women now have several options to reduce their long-term risk of coronary heart disease, osteoporosis, and breast cancer. This analysis suggests that for the great majority of postmenopausal women without a major breast cancer risk factor, long-term HRT remains the dominant alternative, resulting in a greater increase in quality-adjusted life expectancy at a lower cost. However, long-term raloxifene therapy is a cost-effective alternative for postmenopausal women at significantly increased risk of breast cancer and is a cost-effective alternative for women with average breast cancer risk who will not take HRT. Until the results of large scale randomized trials of HRT as primary prevention become available, women and physicians continue to face difficult decisions about postmenopausal therapy. This analysis provides important evidence to make more informed decisions and may make counseling postmenopausal women a little easier.

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